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International Journal of Pharmaceutical Chemistry and Analysis

Journal homepage: https://www.ijpca.org/

Review Article

Review on nanoparticles for topical drug delivery

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ARTICLE INFO

Article history:
Received 14-12-2022
Accepted 05-01-2023
Available online 01-04-2023

Keywords:
Nanoparticles
Transdermal drug delivery
Skin barrier
Surface charge

ABSTRACT

An overview of the use of nanoparticles for topical drug delivery will be given in this review paper. Several experiments have been conducted in the past 25 years to remove some of the obstacles to skin delivery. These investigations have led to a rather modest progress in technology. A more recent method involved increasing the medication's concentration in the carrier to increase drug flow into and through the skin. Hydrophobic and hydrophilic medications can be delivered using nanoparticles, which have the ability to release drugs under regulated conditions over an extended period of time. It also increases patient compliance. Liposomes and solid lipid nanoparticles have the potential to be useful as topical medication delivery methods.

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1. Introduction

Particle sizes for nanoparticles range from 1 to 100 nm, however based on the route of administration, sizes between 50 and 500 nm are suitable for drug delivery. The way a drug is administered has a direct impact on how effective it is. Some medications have a range of optimal concentrations where they will not be harmful or have no therapeutic efficacy.[1] After topical application to the skin's surface, trans-dermal drug delivery systems (TDDS) are controlled-release devices with drugs entrapped inside for the localised treatment of tissues beneath the skin. The medication delivery mechanisms and formulation matrix are different.[2]

Then a no formulations were differing from other conventional topical formulations in the following ways:

1. It has an impermeable occlusive backing film to prevent intensive water loss from the skin.
2. For sustained drug release, matrix of the patch maintains the drug concentration gradient within the device after application.
3. Using an adhesive layer TDDS are kept in place on the skin surface ensuring drug contact with the skin and for continuous drug delivery.[3]

Transdermal drug delivery had been practised for a very long time before TDDS were introduced to the US market in the late 1970s.[4] The use of a nano-particulate delivery technology will improve the penetration of medicinal compounds into and through the skin. Transdermal drug delivery had been practised for a very long time before TDDS were introduced to the US market in the late 1970s.[4] The use of a nano-particulate delivery technology will improve the penetration of medicinal compounds into and through the skin.

2. The Human Skin

With a surface area of between 1.8 and 2.0 m2, our skin is the biggest organ in the body. It primarily has the epidermis, dermis, and hypodermis as its three principal layers (subcutaneous layer). Human skin guards against

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https://doi.org/10.18231/j.ijpca.2023.003
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external threats and controls body temperature and water loss.

When desirable systemic, regional, or local effects are present, this is a common method of drug delivery. Drugs need to have specific properties in order to pass through the stratum corneum and reach a therapeutic concentration in the blood. A variety of techniques have been researched to improve medication transdermal absorption. Iontophoresis, electroporation, ultrasound, and microneedles that open the skin are a few of these cutting-edge permeation-enhancement technologies. Utilizing transdermal nanocarriers is a more recent development. However, the skin acts as a barrier, allowing only modest amounts of a medicine to permeate over time. Designing a drug delivery system is aided by understanding of the anatomy of the skin, the preferred drug, and the delivery technique.

2.1. Routes of drug penetration through the skin

The drug permeates through the skin appendages (hair follicles and sweat glands) by diffusion. The stratum corneum limits the drug permeation through the skin. Three main penetration routes are recognized.

3. The Intercellular Lipid Route

The inter-lamellar zone found in the stratum corneum has less ordered lipids and more flexible hydrophobic chains, which contributes to the non planar voids between crystalline lipid lamellae and the outer membrane of their neighbouring cells. Fluid lipids found in the human skin barrier play a crucial role in the trans epidermal diffusion of lipidic and amphiphilic molecules by occupying the areas needed for their insertion and migration through intercellular lipid layers.[5] The interlamellar gaps' surfaces are covered in hydrophilic molecules that diffuse laterally. Between a lamella and a corneocyte's outer membrane, there is a void that polar molecules can diffuse through.

3.1. The transcellular route

The stratum corneum's intracellular macro molecular matrix was bound by keratin. Although it maintains mechanical stability and the stratum corneum's intactness, it is not actually a diffusive barrier. Transdermal drug delivery does not require transcellular diffusion. The small aqueous transepidermal channels have been seen using confocal laser scanning microscopy. Wrinkles on the skin's surface are related to poor lipid packing in cellular and intercellular areas. Additionally, these areas have the lowest skin resistance for the transportation of hydrophilic substances. By subjecting the stratum corneum to a strong electrical (electroporation/iontophoresis), mechanical (nonoperation/sonophoresis), heat, other appropriate skin penetrating stimuli, the contribution to transdermal drug transport can be increased.

4. Follicular Penetration

Follicular penetration has grown to be a prominent area of interest for drugs that target hair follicles as a result of the enormous skin illnesses that are emerging today. But because follicular orifices make up just 0.1% of the entire skin's surface, this route is not given the same weight as others. However, numerous tests have been carried out to determine the drug's penetration via hair follicles. One of them is the investigation involving topical delivery of polystyrene nanoparticles.[6] In vivo and ex vivo studies on human and pig skin, respectively, showed that polystyrene nanoparticles aggregated in the follicular apertures. Permeation is primarily influenced by time and particle size. The equivalence in penetration between the two membranes was also confirmed by this study. Nanoparticles are effective medication delivery systems and follicle blockers.

5. Main Factors for Nano-Based Delivery System

5.1. Particle size, size distribution & zeta potential

Nanoparticle size and shape significantly affect medication release, physical stability, and cellular uptake. The yield and size distribution of each system are a product of in-process activities and circumstances.[3] The stirring rate, temperature, type and quantity of the dispersion agent, as well as the viscosity of the organic and aqueous phases, are a few of the in-process procedures. Zeta potential is required to keep the dispersion stable.[7]

5.2. Surface properties

The surface charge of the particles helps them bond to the tissue and adhere to cell membranes. Changes in the charge direction affect cellular compartments both in vitro and in vivo. Sulphated proteoglycans with negative charges are found on the surfaces of cells and are crucial for cellular motility, migration, and proliferation. Proteoglycans are made up of a core protein that is connected to one or more glycosaminoglycan side chains to form a structure that protrudes from the cell surface.

Due to electrostatic interactions, nanoparticles bind to biological membranes with a high degree of affinity. Since cell membranes are negatively charged, negatively charged nanoparticles should be repelled by them. Due to the non-specific process of nanoparticles adhering to the cell membrane and forming nanoparticle clusters, there is a high cellular absorption. The adsorption of the negatively charged particles at the positively charged sites by electrostatic contact causes localised neutralisation. This may cause the membrane to bend later and undergo endocytosis for cellular uptake. Nanoparticles can be

directed to particular intracellular targets by altering their surface charges. Systems for transdermal drug delivery are dependent on variables such molecular weight, lipophilicity, and charge.[3] Positively charged nanoparticles will encourage transdermal penetration. For instance, because the skin has a negative surface charge from phosphatidylcholine, cationic chemicals are beneficial for skin permeation.

5.3. Ideal drugs for dermal and transdermal delivery

Due to the selective nature of skin, only some medications can be applied topically. In addition to potency, the drug's physicochemical properties should be favourable for percutaneous delivery. These properties include moderate lipophilicity and low molecular weight.[8] Drug administration for macromolecules like insulin, hGH, or cyclosporine is extremely difficult. Any medication intended for transdermal administration has the following physicochemical properties:

1. Molecular weight less than approximately 1000 Daltons.
2. Affinity for both lipophilic and hydrophilic phases.
3. Low melting point.
4. Should be potent, with short half-life.
5. Non-irritating.

A lively area of research has been developed to overcome the limited skin permeability of xenobiotics. Effectiveness and applicability differ from drug to drug. The process of finding new drugs is still challenging and typically expensive. Technologies for formula change have the advantage of enhancing product performance, patient compliance, and safety. Using gentamicin in biodegradable polyester-based matrices, Nnamani et al. developed and assessed the antimicrobial properties of an alternative non-invasive, practical, and economical TDDS. Nitroglycerin, nicotine, scopolamine, clonidine, fentanyl, 17–oestradiol, testosterone, curcumin (Curcuma longa), and other medications have also been developed for dermal and transdermal delivery.

6. Topical Applications of Nanoparticles

6.1. ACNE

The most common skin condition is acne vulgaris. The face, back, and chest are examples of body parts with a high concentration of sebaceous follicles and are related with an elevated rate of sebum secretion, which results in mild to severe inflammatory lesions.[9] It might be mild, moderate, or severe depending on the number and type of lesions. The kind of skin, stage, and severity of the disease all influence the available treatments. In general, mild to moderate acne is best treated with topical medicine, whereas severe cases are better treated with systemic therapy. Antibiotics, retinoids (vitamin A), and mixtures are examples of topical medications. The retinoids irritate the skin and lead to dryness, exfoliation, photosensitivity, and hyper pigmentation as a result. Antibiotic use over an extended period of time may cause bacterial resistance. Due to these issues, nanoparticles are being created to deliver these medications into the skin in a targeted and sustained manner. The main criterion for selecting acne medication formulations using nanoparticles is increased efficacy with minimal topical side effects. Effectiveness, toleration, compliance, and cosmetic acceptability should all be present.[10,11]

6.2. Infection

Infectious illnesses and microorganisms with medication resistance are both spreading rapidly. The morbidity and mortality of microbial infections remain high despite extensive understanding of the microbial aetiology and antibiotic therapy. The use of nanoparticle systems as antibacterial and anti-infective drugs has recently been covered in a review.[12] For instance, a study demonstrates that AgNPsas antimicrobials can bind to proteins in bacterial cell membranes that contain sulphur, causing the bacteria to die as a result of increased permeability. The overall surface area of the nanoparticles affects their antibacterial activities; smaller particles with higher surface-to-volume ratios have broader antibacterial activity.[13] AuNPs have optical near-infrared absorption and can kill bacteria by photo thermally heating them. AuNPs cause breaches in the cell wall, which cause the cell's contents to leak out and cause cell death. It is plausible that AuNPs attach to bacterial DNA and prevent DNA uncoiling and transcription. Its stable conjugates coat with anti-microbials has demonstrated bactericidal effect against both Gram-positive and Gram-negative microscopic organisms. Additionally, the antibacterial effects of other metal oxide nanoparticles have been investigated. Halogen-treated magnesium oxide (MgO) nanoparticles are one example of antibacterial action against microorganisms and spores. Because it has a stronger affinity for the amines and carboxyl groups on the cell surface of bacteria, copper oxide (CuO) nanoparticles have a strong antibacterial effect against Bacillus subtilis.

6.3. Skin cancer

Despite not being the deadliest kind of cancer, skin cancer is the most prevalent one. Basal cell carcinoma and squamous cell carcinoma, which together account for over 2.8 million and 700,000 incidences of skin cancer in the United States, respectively, per year.[14,15] On the other hand, malignant melanoma accounts for the vast majority of skin cancer deaths despite representing as

it were a very small proportion of skin malignancies (74,000 U.S. cases annually).[16] In the case of melanoma, excision will involve extensive surgeries with profound dissections and wide margins, frequently requiring soft tissue reconstruction. Excision is currently the standard treatment for localised skin cancers. Additionally, skin malignancies have the potential to spread to nearby lymph nodes and far-off places. Nanoparticles may deliver focused and efficient chemotherapeutic transport to these locations, enhancing the efficacy of the therapy. Liposomes, SLNs, polymeric nanospheres, and dendrimers are a few examples of nanoparticles utilised in topical delivery systems for the treatment of skin cancer. Excellent circulation, penetration, and diffusion characteristics are displayed by liposomes. Early studies claim that liposomes are preserved near tumour arteries in the interstitial fluid of tumours. Several liposome-based medication delivery formulations are available to treat cancer. There are more chemotherapeutic drug liposomal carriers that are now undergoing clinical studies. Small interfering RNA is successfully delivered by cationic liposomes (si RNA). New methods have been devised to incorporate anticancer medicines into a wide range of diagnostic nanoparticles. SLNs can offer command. Additionally, skin malignancies have the potential to spread to nearby lymph nodes and far-off places. Nanoparticles may deliver focused and efficient chemotherapeutic transport to these locations, enhancing the efficacy of the therapy. Liposomes, SLNs, polymeric nanospheres, and dendrimers are a few examples of nanoparticles utilised in topical delivery systems for the treatment of skin cancer. Excellent circulation, penetration, and diffusion characteristics are displayed by liposomes. Early studies claim that liposomes are preserved near tumour arteries in the interstitial fluid of tumours. Several liposome-based medication delivery formulations are available to treat cancer. There are more chemotherapeutic drug liposomal carriers that are now undergoing clinical studies. Small interfering RNA is successfully delivered by cationic liposomes (si RNA). New methods have been devised to incorporate anticancer medicines into a wide range of diagnostic nanoparticles. SLNs can offer command. Additionally, skin malignancies have the potential to spread to nearby lymph nodes and far-off places. Nanoparticles may deliver focused and efficient chemotherapeutic transport to these locations, enhancing the efficacy of the therapy. Liposomes, SLNs, polymeric nanospheres, and dendrimers are a few examples of nanoparticles utilised in topical delivery systems for the treatment of skin cancer. Excellent circulation, penetration, and diffusion characteristics are displayed by liposomes. Early studies claim that liposomes are preserved near tumour arteries in the interstitial fluid of tumours. Several liposome-based medication delivery formulations are available to treat cancer. There are more chemotherapeutic drug liposomal carriers that are now undergoing clinical studies. Small interfering RNA is successfully delivered by cationic liposomes (si RNA). New methods have been devised to incorporate anticancer medicines into a wide range of diagnostic nanoparticles. Drug release kinetics can be regulated by SLNs, and they can shield medications against deterioration. In vitro and in vivo studies on docetaxel-loaded SLNs have revealed enhanced activity against colorectal (C-26) and malignant melanoma (A-375) cell lines.[17]

6.4. Inflammatory diseases

Inflammation is group of dermatologic illness processes and influences skin's barrier function. This inflammation leads to entry of microbes, allergens and other stimuli, which can cause further disruption. Actual pathogenesis of some inflammation is not known. Colonization of microbes lead to cutaneous inflammation with varying degrees of physiological and aesthetic impact, such aseczema, psoriasis, atopic dermatitis, rosacea, lichen planus, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis. Nanotechnology has provided anovel approach for the delivery of drugs that can reduce inflammation and its effects on the skin's barrier function. For example, Kilfoyle and co-workers have shown that Tyrospheres are able to provide dose-controlled delivery ofan anti- proliferative agent paclitaxel. It deposited in the epidermis. So that we can use paclitaxel-loaded Tyrospheres for the treatment of psoriasis.[18] Compared to liposomes and other surfactant micelles, polymeric micelles are often more stable in blood. Polymeric micelle systems can be utilised to co-deliver two or more medications for combinational treatment modalities, such as radiation therapy and anticancer medications, due to their enormous size. It showed that, compared to animals given with free medication, therapy with drug-loaded polymeric micelles inhibited tumour growth and improved survival rates. Additionally, dendrimers have been employed in cutaneous squamous cell carcinoma and melanoma immunotherapies. Dendronized polymers, which are linear polymers with dendrons at each repeat unit, are a novel class of molecules that have been produced in response to the difficult controlled release of dendrimers. Dendrimers are composed of monodisperse wedge-shaped portions called dendrons. The three characteristics they share are an initiator core, internal branching units, and a function of generation (G) level. The delivery offered by these compounds is focused and ongoing.

6.5. Cosmetics

In cosmetic dermatology, the main skin issues include dry skin, oily skin, hyperpigmentation, hypopigmentation, vascular malformations, and photoaging. For this condition,

many different formulations are created. The safety of using nanoparticles topically has generated much debate over whether they can cause harm to healthy skin cells by inducing the formation of free radicals or by evading immune system defence mechanisms, forming protein complexes, or getting absorbed systemically. This debate is particularly pronounced in relation to the use of nanoparticles in sunscreens (which are directed as drugs within the U.S.).

Due to their ability to reflect UV light, ZnO and TiO2 nanoparticles have historically been employed in sunscreens. Recently, ZnO and TiO2 nanoparticles have been improved to be more transparent, thinner, and easier to mix while maintaining their effectiveness against UV light.[19] In any event, it is necessary to investigate their toxicological profiles because smaller particles are likely to have unique chemical, optical, magnetic, and structural characteristics. Due to the security issues with metal nanoparticles in sunscreens, Cross et al. conducted a penetration research using a Franz-cell diffusion setup. ZnO nanoparticles were administered topically to cadaver skin in this study, and after 24 hours, 0.03% of the treated ZnO nanoparticles were detected in the upper SC and epidermis. According to these data, it is unexpected that ZnO nanoparticles infiltrated the dermis of this model through the epidermis. For the treatment of hyperpigmented wounds and aged skin, vitamin A has been studied. Retinoic acid derivatives like retin aldehyde and retinol are significantly less irritating, while retinylpalmitate and acetic acid derivative esters cause slight irritation because they are the natural storage forms of vitamin A in the skin. Retinoic acid derivatives can sometimes cause burning, scaling, and disturbance, which limits the acceptance by patients. Yamaguchi has created nano-particles to reduce adverse effects and boost efficacy. Etal[20] investigated the effects of ali-transretinoic corrosive, or atRA, nanoscale tretinoin on photodamaged skin. It displays a reduction in inflammation and irritation.According to these data, it is unexpected that ZnO nanoparticles infiltrated the dermis of this model through the epidermis. For the treatment of hyperpigmented wounds and aged skin, vitamin A has been studied. Retinoic acid derivatives like retin aldehyde and retinol are significantly less irritating, while retinylpalmitate and acetic acid derivative esters cause slight irritation because they are the natural storage forms of vitamin A in the skin. Retinoic acid derivatives can sometimes cause burning, scaling, and disturbance, which limits the acceptance by patients. Yamaguchi has created nano-particles to reduce adverse effects and boost efficacy. Etal[20] investigated the effects of ali-transretinoic corrosive, or atRA, nanoscale tretinoin on photodamaged skin. It displays a reduction in inflammation and irritation.

The natural antioxidant coenzyme Q10 is often used in cosmetics. It is a provitamin that is lipid-soluble and less water-soluble. Drug delivery devices like SLNs and liposomes are therefore employed to aid in the penetration into the deeper layers of skin. Octyl methoxycinnamate, also known as ethylhexyl methoxycinnamate, is a key component of sunscreens. In order to calculate the percutaneous absorption, Puglia et al.[21] combined two substances, OMC and diethyltoluamide, into SLNs. This study provided proof that the topical administration of SLN delivery systems could improve their security and efficacy while lowering their systemic absorption for this application. When OMC is exposed to sunshine, it can switch to its cis-form, which lowers the effectiveness of its UVB filtering.

6.6. Ophthalmology

Barriers such as the ocular surface epithelium, tear film, and blood-ocular block the penetration of medications when they are applied topically to the eye. When it comes to ocular drug delivery, nanoparticles exhibit the following traits:

6.7. Should increase the penetration of large, poorly water-soluble molecules

Example: The immunosuppressive drugs used in the delivery of glucocorticoid for the treatment of immune-related diseases.

6.8. Increase the contact time of the drug with its target tissue

Example: Brimonidine used in the treatment of glaucoma or corticosteroids for autoimmune uveitis.

7. It Reduces Side Effects of Highly Potent Drugs

7.1. Increase patient compliance

Ex: The anterior segment of the eye will be negatively impacted by the daily use of eye drops for glaucoma.[10] Timolol eye drops with nanoparticles compared favorably to timolol eye drops without them in Wadhawa et al.[22] 's study. He said that there was a notable drop in intraocular pressure without any irritated rabbit eyes. Heal of chronic wounds. Example: The anterior segment of the eye will be negatively impacted by the daily use of eye drops for glaucoma.[10] Timolol eye drops with nanoparticles compared favourably to timolol eye drops without them in Wadhawaet al.[22] 's study. He said that there was a notable drop in intraocular pressure without any irritated rabbit eyes. Heal of chronic wounds.

Infection has always been the primary focus of topical treatment for cutaneous wounds, but recently, researchers have created new multifunctional nano-systems that have the potential to have more extensive therapeutic effects.

When the typical wound healing cascade is not successfully completed by chronic wounds, wound closure is delayed or fails altogether. These stubborn wounds frequently coexist with diabetes, infection, and peripheral artery disease. Chronic wounds are not generally treated. Surgical debridement to remove dead tissue and debris, hyperbaric oxygen therapy, skin replacements, vacuum-assisted wound closure, topical medications, and compression bandages are some of the treatment options. Nanoparticles have been designed to transport silver and morphine to chronic wounds in order to reduce bacterial colonisation and discomfort. In order to shield the therapeutic agents from degradation in the highly proteolytic wound environment, the medicine is also encased in nanoparticles. Nanoparticulate technologies have also been used to stabilise and release nitric oxide, a vasoactive substance, to treat ischemia. Cerium oxide nanoparticles can be applied topically to treat full-thickness skin wounds in mice, according to Chigurupatiet al.[23] It functions by a process that speeds up different skin cells' migration and proliferation. By the aforementioned process, cerium nanoparticles entered the damaged tissue and lessened protein and cellular membrane oxidative damage. Additionally, the use of curcumin for antibacterial and wound healing purposes has been studied. In an in-vivo murine wound model, Krausz et al.[24] found that curcumin-loaded nanoparticles reduced microbial growth and improved wound healing.

8. Conclusion

Nanoparticles have the ability to carry medications through the skin barrier successfully, according to studies done on them over the past two decades. In addition to polymeric and metal-based nanoparticles, drug delivery systems like liposomes and solid lipid nanoparticles have potential value as topical drug delivery systems. Electro spun nano fibres have also demonstrated excellent effectiveness in the field as antibacterial dressings and in the treatment of wounds. Advanced clinical research have shown that fibermats and nanoparticles have had a limited therapeutic impact as topical or transdermal medication delivery methods. A very thorough global research effort into items utilised in therapeutic settings appears to have developed slowly. Although topical applications of nanotechnology have shown promise, more focus needs to be placed on quantitative studies that can link nanoparticle exposure and dose to penetration and therapeutic efficacy. Although topical applications of nanotechnology have shown promise, more focus needs to be placed on quantitative studies that can link nanoparticle exposure and dose to penetration and therapeutic efficacy. More research is being done on drug targeting and nanoparticle toxicity. Additionally, evaluations of the effectiveness of nanoparticle penetration in healthy skin versus inflamed skin are sparse. Although topical applications of nanotechnology have shown promise, more focus needs to be placed on quantitative studies that can link nanoparticle exposure and dose to penetration and therapeutic efficacy. Although topical applications of nanotechnology have shown promise, more focus needs to be placed on quantitative studies that can link nanoparticle exposure and dose to penetration and therapeutic efficacy. More research is being done on drug targeting and nanoparticle toxicity. Additionally, evaluations of the effectiveness of nanoparticle penetration in healthy skin versus inflamed skin are sparse. Less is known about the methods used to move nanoparticles across the three primary layers of skin. The fact that so few studies use commercially viable controls is another intriguing finding. For instance, rather than using the current clinical gold standard as a benchmark, researchers frequently compare the effects of drug formulations containing nanoparticles to those of drug-free formulations. As a result, there are a lot of intriguing unresolved problems and technological difficulties that offer a lot of room for additional future research.

9. Source of Funding

None.

10. Conflict of Interest

None.

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Cite this article: Shaikh AA, Pawar JB, Anbhule SJ, Kakade VV. Review on nanoparticles for topical drug delivery. *Int J Pharm Chem Anal* 2023;10(1):8-14.