
STRATEGY OF TOPICAL VACCINATION WITH NANOPARTICLES

Sanchita Hanumant Gavali*¹, Meera Deokar*²

*¹Late Laxmibai Phadtare College Of Pharmacy Kalamb, India.

*²Assistant Professor Of, Late Laxmibai Phadtare College Of Pharmacy Kalamb, India.

ABSTRACT

Topical vaccination represents a novel and promising approach to immunization, offering a non-invasive route for the delivery of vaccines directly to mucosal surfaces, which are critical sites for pathogen entry. This review comprehensively explores the strategic use of nanoparticles as innovative carriers for topical vaccine formulations. The review highlights the mechanisms through which nanoparticles can modulate immune responses, such as facilitating the uptake of antigens by dendritic cells, promoting local and systemic immunity, and enhancing the duration of immune memory. We address key challenges associated with the development of nanoparticle-based topical vaccines, such as formulation stability, penetration through the skin or mucosal barriers, and regulatory considerations. Recent advancements in nanoparticle technology, including smart nanoparticles capable of controlled release and stimuli-responsive systems, are also discussed, showcasing their potential to optimize vaccine delivery and efficacy.

Keywords: Topical Vaccination, Nanoparticles, Vaccine Delivery System, Liposomes, Formulation Challenges, Vaccine Stability, Bio Compatibility.

I. INTRODUCTION

Vaccination is one of the most effective public health interventions for preventing infectious diseases. Traditionally, vaccines are administered via parenteral routes, such as intramuscular or subcutaneous injections. While effective, these methods often face challenges, including patient discomfort, logistical barriers in vaccine distribution, and variable immune responses. Recent advancements in immunization strategies have led to the exploration of alternative delivery routes, particularly topical vaccination, which aims to administer vaccines directly to mucosal surfaces—the primary entry points for many pathogens.

Topical vaccination offers several advantages, including ease of administration, reduced risk of needle-related injuries, and the potential for improved patient compliance. Mucosal surfaces, such as those in the respiratory, gastrointestinal, and urogenital tracts, are equipped with specialized immune cells that play a crucial role in the development of both local and systemic immunity. Nanoparticles have emerged as powerful tools in vaccine development and delivery, owing to their unique physicochemical properties that facilitate enhanced antigen presentation and immune modulation.

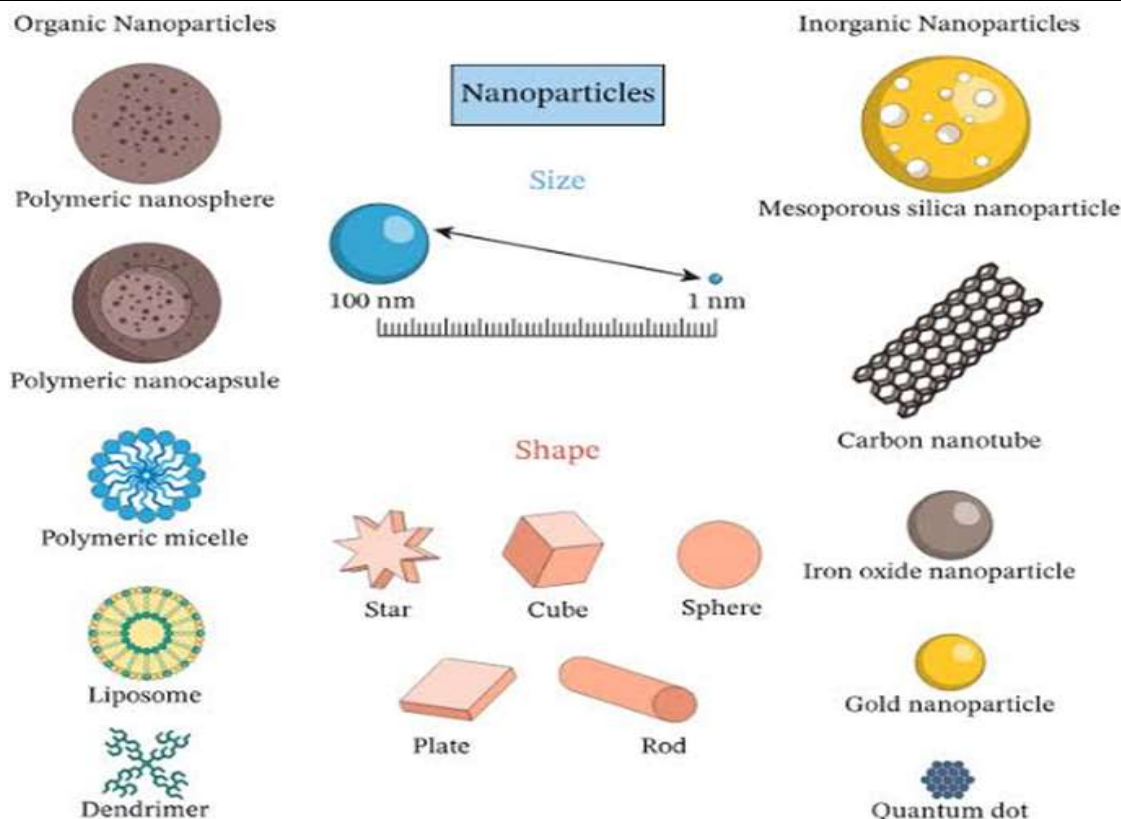
Nanoparticles can be engineered to optimize targeting and uptake by immune cells. Surface modifications, such as the incorporation of ligands or adjuvants, can further improve their ability to interact with specific immune cell populations, thus facilitating more effective antigen presentation and enhancing both local and systemic immunity. This targeted approach not only maximizes vaccine efficacy but also minimizes the risk of adverse effects, making nanoparticles a promising solution for overcoming the limitations associated with traditional vaccine formulations.

Nanoparticles, due to their unique size, surface properties, and ability to encapsulate diverse bioactive molecules, have revolutionized vaccine delivery. Their small size (typically 1-1000 nanometers) allows for enhanced permeability and retention at target sites, while their large surface area provides opportunities for functionalization and targeted delivery. These attributes facilitate improved stability and bioavailability of vaccine antigens, addressing one of the critical challenges in vaccine formulation.

Nanoparticles:

Nanoparticles are extremely small particles that typically have a size range of 1 to 100 nanometers (nm). At this scale, the ratio of surface area to volume is greatly increased, which affects reactivity and other physical properties.

Their unique properties arise from their small size and high surface area-to-volume ratio, leading to distinct physical and chemical behaviors compared to bulk materials.



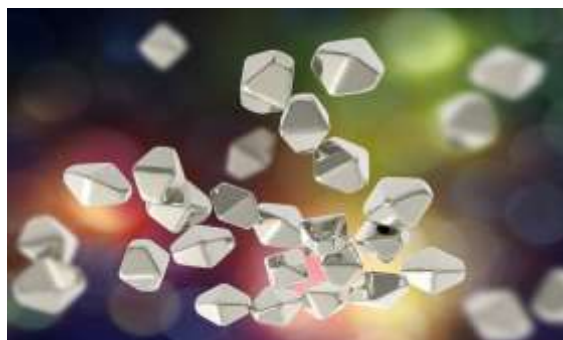
Types of Nanoparticles:-

1. Metallic Nanoparticles

These nanoparticles are nanosized metals that range in size from 10 to 100 nm. They have functional groups that allow them to bind with other beneficial compounds, like drugs.

The most common types of metal nanoparticles include silver, gold, palladium, titanium, zinc, and copper nanoparticles.

Metal nanoparticles are utilized across several research fields, including the detection and imaging of biomolecules and in environmental and bioanalytical applications. For example, gold nanoparticles are used to coat the sample before scanning electron microscope (SEM) analysis to enhance SEM and produce high-quality electron microscopy images. Metal nanoparticles also have important applications in drug delivery when they are extensively used for a variety of therapeutic agencies, including antibodies, nucleic acids, peptides, and more.

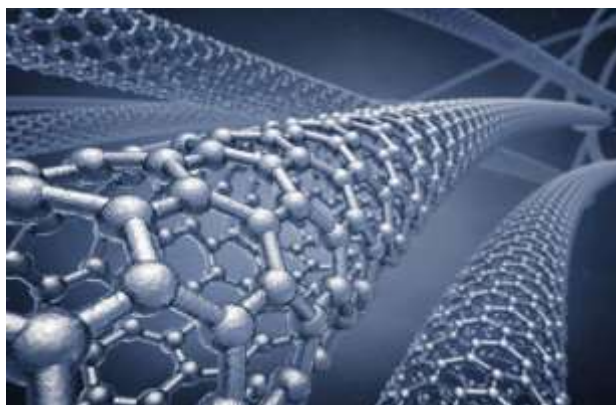


2. Carbon based nanoparticles:-

These nanoparticles can be classified as nanotubes, graphene, graphene oxide, and fullerenes. They are easy to modify and have excellent electrical and thermal properties. The carbon units in these structures have a pentagonal and hexagonal arrangement. The applications of these carbon-based nanoparticles are diverse. They

have many commercial applications due to their electrical conductivity, structure, high strength, and electron affinity.

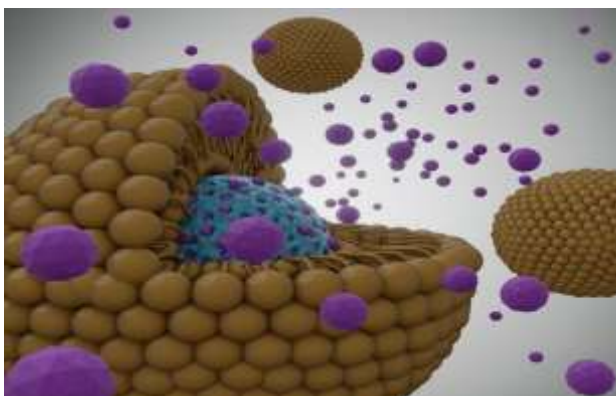
CNTs can be classified into single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). CNTs are unique as they are thermally conductive along the length and non-conductive across the tube.



3. Ceramic Nanoparticles:-

Ceramic nanoparticles are primarily made up of oxides, carbides, phosphates and carbonates of metals and metalloids such as calcium, titanium, silicon, etc.

One of the most important applications of ceramic nanoparticles is in drug delivery. By controlling their specific characteristics like size, surface area, porosity, and surface area-to-volume ratio, these nanomaterials perform as good drug delivery agents. They have been used effectively as a drug delivery system for several diseases like bacterial infections, glaucoma, and cancer. More recently, scientists have developed these nanoparticles for use in bone repair.



4. Lipid Nanoparticles:-

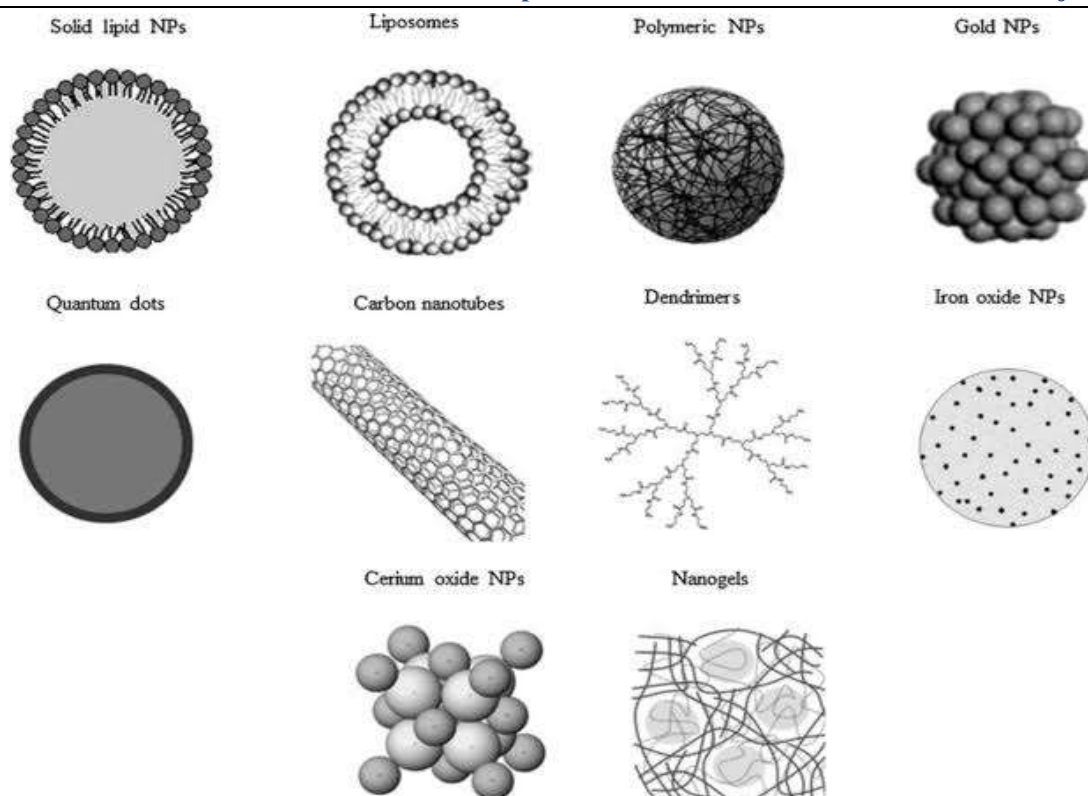
Lipid nanoparticles are generally spherical, with a diameter ranging from 10 to 100nm. Their structure consists of a solid core made of lipids and a matrix containing soluble lipophilic molecules, and surfactants and emulsifiers stabilize the external core.

This type of nanoparticle has applications in the biomedical field as drug carriers and RNA release in cancer therapy. In particular, they have been successful in transporting drugs and oligonucleotides that are poorly water-soluble in gene therapy applications.

5. Polymeric Nanoparticles:-

Polymeric nanoparticles are organic-based nanoparticles. Depending upon the preparation method, these types of nanoparticles have structures shaped like nanocapsules or nanospheres.

A nanosphere nanoparticle has a matrix-like structure, whereas nanocapsules have core-shell morphology. In nanosphere polymeric nanoparticles, the active compounds and the polymer are uniformly dispersed, while in nanocapsule nanoparticles, the active compounds are confined and surrounded by a polymer shell.



Advantages of Nanoparticles:

1. **Increased Surface Area:** Nanoparticles have a high surface area-to-volume ratio, enhancing their reactivity and effectiveness in applications like catalysis and drug delivery.
2. **Enhanced Properties:** Nanoparticles often exhibit unique physical and chemical properties compared to their bulk counterparts, such as increased strength, lighter weight, improved electrical conductivity, and better optical characteristics.
3. **Targeted Drug Delivery:** In medicine, nanoparticles can be engineered to target specific cells or tissues, allowing for more effective drug delivery while minimizing side effects.
4. **Improved Detection:** In diagnostics, nanoparticles can enhance the sensitivity and specificity of detection methods, making it easier to identify diseases at an early stage.
5. **Environmental Remediation:** Nanoparticles can be used to remove pollutants from water and air, helping to improve environmental health.
6. **Energy Efficiency:** In energy applications, nanoparticles can improve the efficiency of solar cells, batteries, and fuel cells, leading to better energy storage and conversion technologies.
7. **Biocompatibility:** Many nanoparticles can be designed to be biocompatible, making them suitable for use in medical implants and devices.
8. **Versatility:** Nanoparticles can be made from various materials, including metals, oxides, and polymers, allowing for a wide range of applications and customization.
9. **Antimicrobial Properties:** Certain nanoparticles, like silver nanoparticles, possess natural antimicrobial properties, making them useful in medical devices, coatings, and wound dressings.
10. **Sustainability:** Nanoparticles can contribute to more sustainable practices, such as reducing the amount of raw materials needed in manufacturing processes and enabling cleaner production techniques.

Applications of Nanoparticles:-

1. Drug delivery

Nanoparticles are used to deliver drugs to specific sites in the body, which can reduce side effects. Dendrimers are a type of nanoparticle that are often used in drug delivery systems.

2. Biomedical imaging

Nanoparticles are used in medical imaging because they are small enough to enter individual cells.

3. Food packaging

Nanoparticles can be used to create food packaging that keeps food fresh longer and food additives that improve the flavor and nutritional value of food.

4. Cancer Therapy:

Targeted therapy using nanoparticles helps in the selective destruction of cancer cells.

5. Imaging and Diagnostics:

Quantum dots and gold nanoparticles are used as contrast agents in imaging techniques like MRI and CT scans.

6. Water Treatment:

Nanoparticles are effective in removing contaminants from water, including heavy metals and pathogens.

7. Pollution Control:

Nanocatalysts can accelerate chemical reactions that break down pollutants in the air and water.

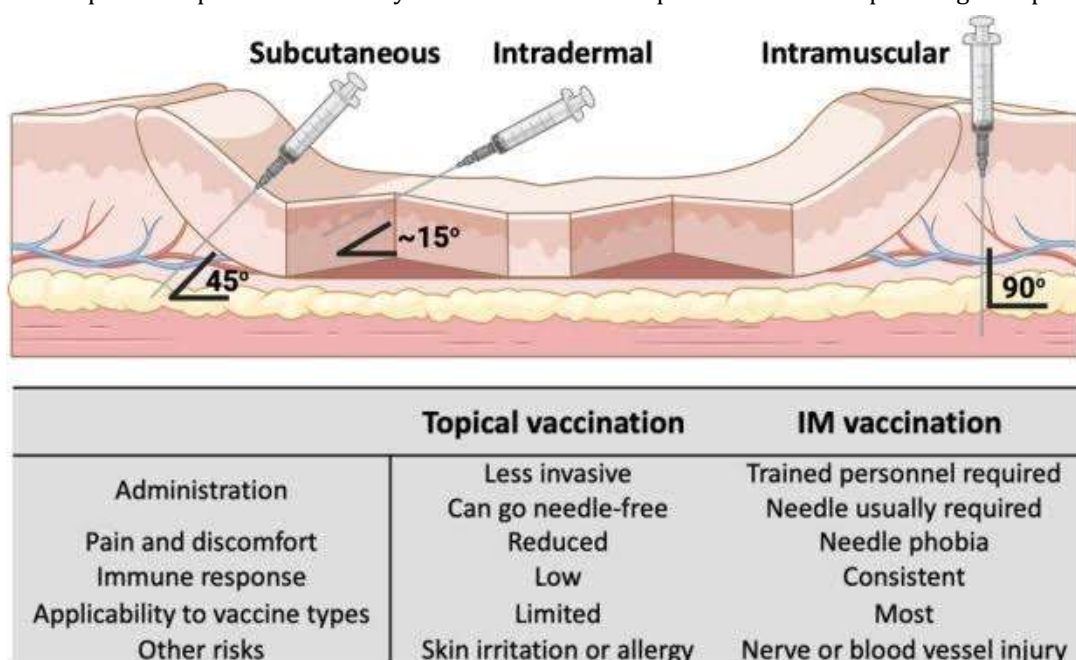
Topical vaccination:

Topical vaccination is the administration of vaccines through the skin or mucous membranes, rather than through traditional methods like intramuscular or subcutaneous injections. This approach aims to enhance the immune response and improve vaccine efficacy, particularly for diseases that are typically transmitted via mucosal surfaces, such as respiratory infections or gastrointestinal diseases.

Topical vaccines are a new approach to vaccination that involves introducing a vaccine into the skin or mucosa without the use of needles or expensive delivery devices. The skin is an accessible organ that can be used to deliver vaccines in a cost-effective and simple way.

Topical vaccines have several potential benefits, including:

- Needle-free: Topical vaccines can be administered without the use of needles.
- Immune response: Topical vaccines may be able to induce a superior immune response against pathogens.

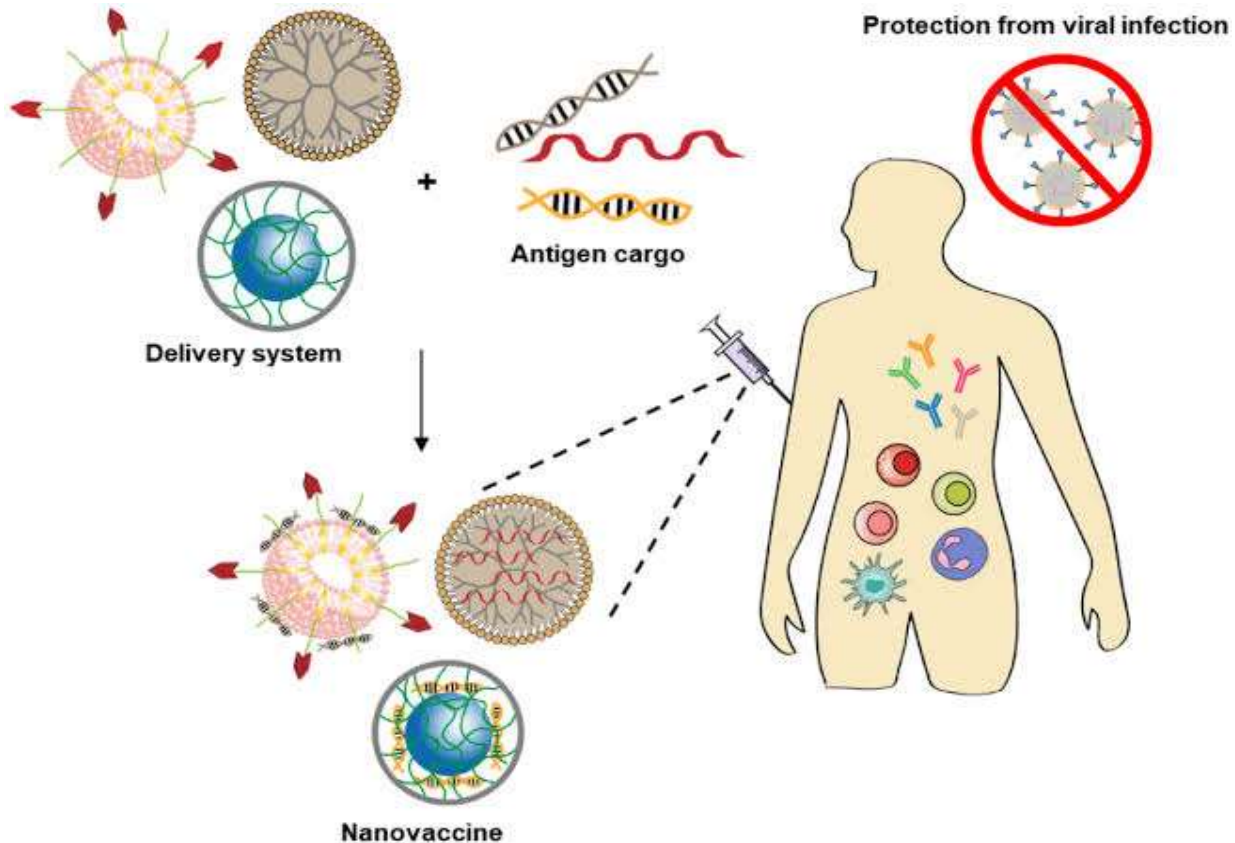


Mechanism of Action:

Immune Activation

Adjuvanticity: Many nanoparticles can act as adjuvants themselves, enhancing the immune response by activating various immune pathways.

Antigen Presentation: Once nanoparticles are taken up by antigen-presenting cells (APCs), they promote the processing and presentation of antigens to T cells, thus initiating adaptive immunity.



B. Cell Activation and Antibody Production

Activation of B Cells: T helper cells stimulate B cells, leading to their activation, proliferation, and differentiation into plasma cells that produce antibodies.

Class Switching: This process allows B cells to produce different classes of antibodies (e.g., IgA, IgG), enhancing the immune response.

Induction of Immune Memory

Memory Cell Formation: Some activated T and B cells differentiate into memory cells, allowing for a more rapid and robust response upon subsequent exposure to the same antigen.

Long-lasting Immunity: This memory formation is crucial for long-term protection against infections.

Antigen Presentation and Adaptive Immunity

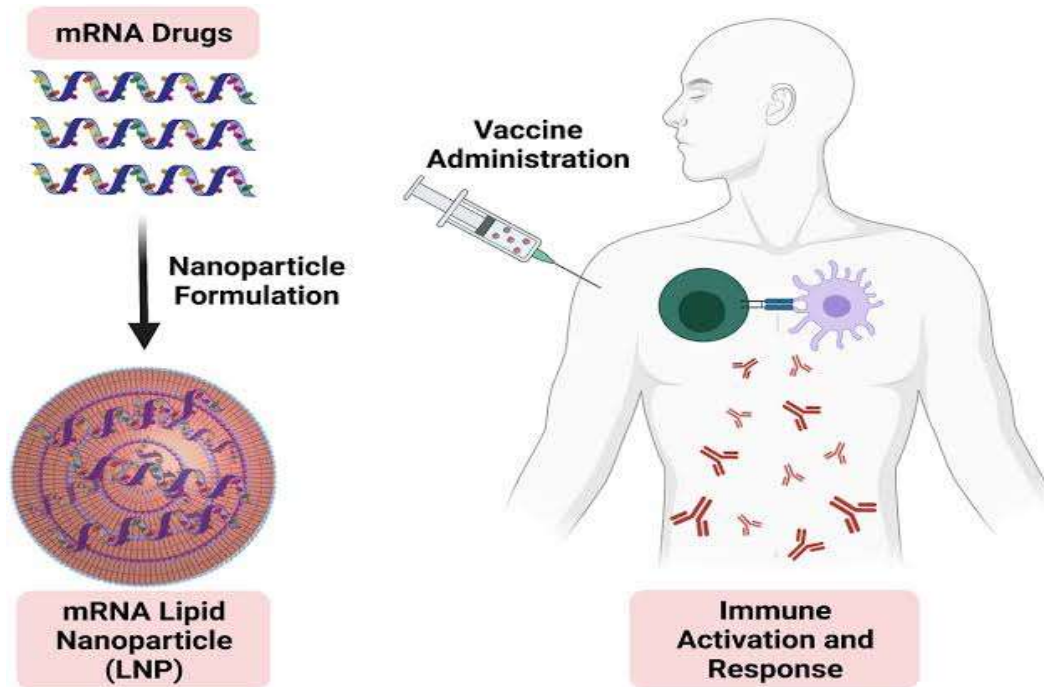
Dendritic Cell Maturation: After uptake, nanoparticles can induce the maturation of dendritic cells, enhancing their ability to present antigens and activate T cells.

T Cell Activation: Activated dendritic cells migrate to lymph nodes, where they present processed antigens to naïve T cells, leading to their activation and differentiation into effector T cells (e.g., CD4+ helper T cells and CD8+ cytotoxic T cells).

Activation of Innate Immunity

Recognition by Immune Cells: Nanoparticles can stimulate pattern recognition receptors (PRRs) on APCs, such as Toll-like receptors (TLRs), leading to the activation of the innate immune response.

Cytokine Production: The activation of innate immune pathways results in the release of pro-inflammatory cytokines (e.g., IL-1, IL-6) that recruit and activate various immune cells to the site of application.

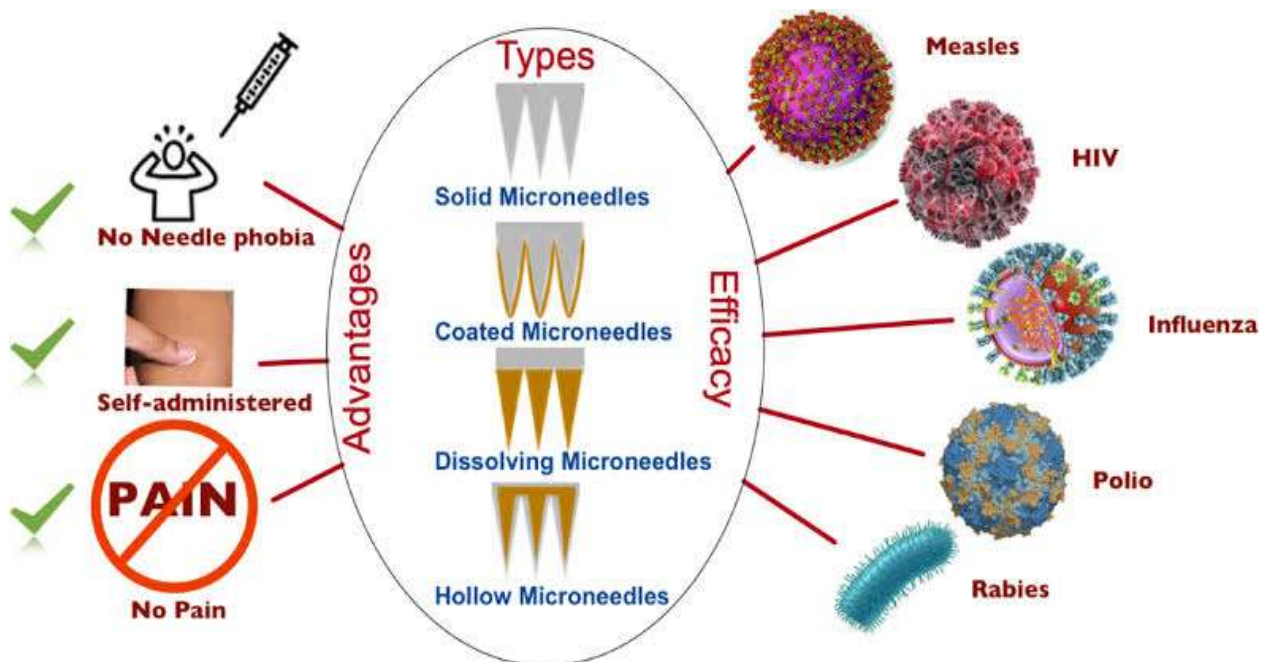


Administration routes

Microneedle Patches:

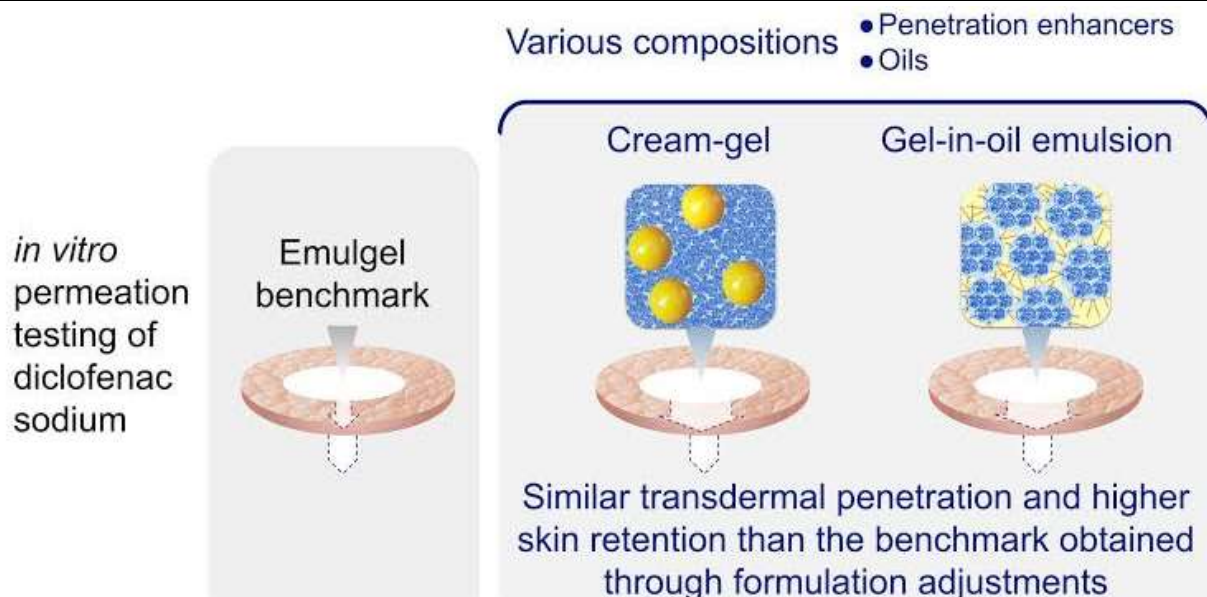
Microneedle technology involves skin puncturing and has emerged as an innovative approach for drug delivery and cosmetic applications. MNs offer advantages over traditional injections, such as reduced pain, infection risks, and improved control of drug delivery.

Microneedles are small needles that penetrate the outer layer of the skin (epidermis) to deliver vaccines directly into the dermis. This method can enhance the uptake of antigens by immune cells (such as dendritic cells) located in the skin, promoting a robust immune response without causing pain.



Topical Creams or Gels:

Vaccines formulated into creams or gels can be applied directly to the skin. Nanoparticles or permeation enhancers may be included to facilitate better absorption through the skin barrier.



Challenges associated with the development of Nanoparticles based topical vaccination:-

Developing nanoparticles-based topical vaccines presents several challenges, which can be categorized into technical, biological, and regulatory aspects.

1. Technical Challenges

- **Nanoparticle Design and Formulation:** Designing nanoparticles with optimal size, shape, and surface properties is complex. These factors influence their stability, immune response, and ability to penetrate the skin barrier.
- **Stability and Storage:** Maintaining the stability of nanoparticles during storage and transportation is crucial. They may degrade or agglomerate over time, affecting their efficacy.
- **Controlled Release:** Achieving a controlled and sustained release of antigens from nanoparticles is essential to elicit a robust immune response. This requires careful formulation and selection of materials.

2. Biological Challenges:-

- **Skin Penetration:** The skin acts as a formidable barrier. Developing nanoparticles that can effectively penetrate the stratum corneum without causing irritation is a significant hurdle.
- **Immune Response:** Ensuring that the nanoparticles induce a strong and appropriate immune response without causing adverse effects (like inflammation or allergic reactions) is critical. The type of immune response (humoral vs. cellular) must be carefully controlled.
- **Bioavailability:** The bioavailability of antigens delivered via nanoparticles needs to be sufficient to elicit an effective immune response. Factors like enzymatic degradation and metabolic processes can affect this.

3. Regulatory Challenges:-

- **Safety and Efficacy Evaluation:** Establishing the safety and efficacy of nanoparticles-based vaccines requires extensive preclinical and clinical testing. The unique characteristics of nanoparticles may necessitate new testing protocols.
- **Standardization and Quality Control:** Ensuring consistent production quality and batch-to-batch reproducibility of nanoparticles is essential for regulatory approval. This includes establishing standardized methods for characterization.
- **Regulatory Framework:** Current regulatory frameworks may not adequately address the unique aspects of nanoparticle-based vaccines. This could result in longer approval times and uncertainty regarding compliance.

4. Manufacturing Challenges:-

- **Scalability:** Transitioning from laboratory-scale production to large-scale manufacturing of nanoparticles is complex and may face issues related to scalability and cost-effectiveness.

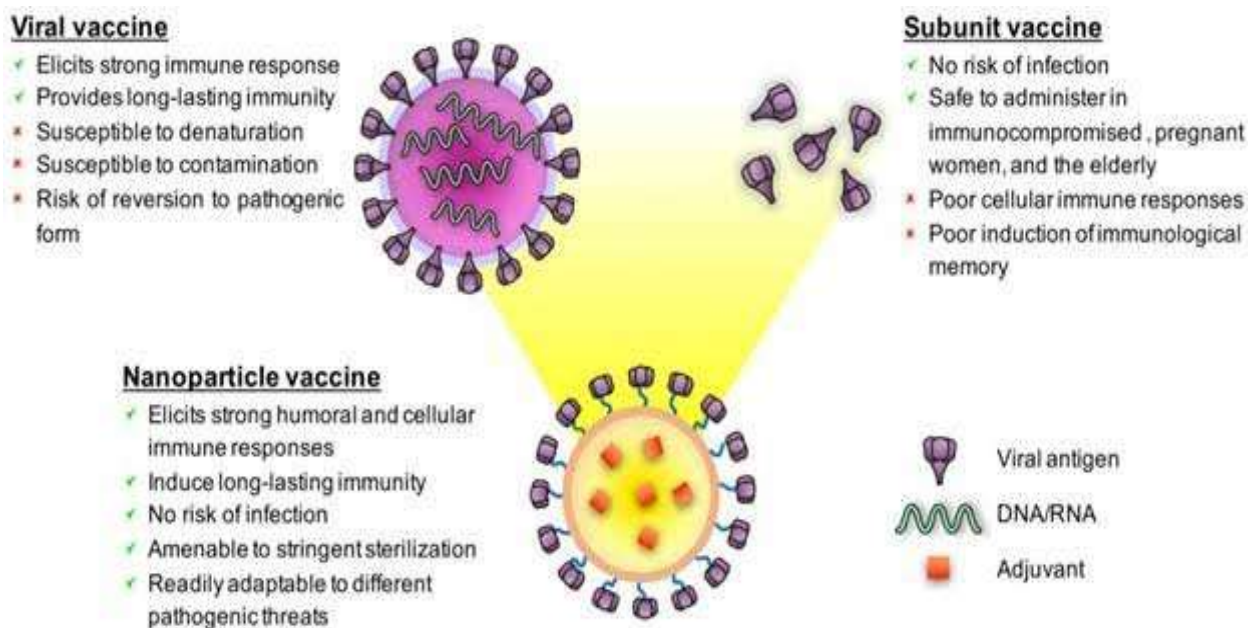
- Material Selection: Choosing biocompatible and biodegradable materials that can be safely used in humans while also being cost-effective can be challenging.

5. Patient Acceptance and Education:-

- Public Perception: Gaining public trust and acceptance of nanoparticle-based vaccines is essential. Misinformation about nanoparticles and vaccines can hinder uptake.
- Education: Educating healthcare providers and patients about the benefits and risks of topical nanoparticle vaccines is necessary to promote informed decision-making.

Benefits of topical vaccination with nanoparticles:-

Topical vaccination using nanoparticles has several promising benefits, particularly in enhancing vaccine delivery and efficacy.



1. Improved Delivery: Nanoparticles can facilitate the targeted delivery of antigens directly to immune cells in the skin, enhancing the local immune response.
2. Enhanced Stability: Nanoparticles can stabilize sensitive vaccine components, protecting them from degradation due to environmental factors such as temperature and humidity.
3. Controlled Release: The use of nanoparticles allows for a controlled release of the vaccine over time, which can prolong the immune response and reduce the need for booster doses.
4. Reduced Side Effects: Topical administration can minimize systemic exposure, potentially leading to fewer side effects compared to traditional intramuscular or subcutaneous injections.
5. Pain-Free Administration: Topical vaccination is less invasive and can be administered painlessly, improving patient compliance and acceptance, especially in populations averse to needles.
6. Adjuvant Properties: Certain nanoparticles can act as adjuvants, enhancing the immune response to the vaccine by stimulating local immune cells.
7. Ease of Administration: Topical vaccines can be self-administered, reducing the need for healthcare professional involvement and potentially increasing vaccination rates.
8. Versatility: Nanoparticles can be designed to carry a variety of antigens, allowing for the development of vaccines against various pathogens and diseases.
9. Localized Immune Response: Targeting the skin can elicit a strong mucosal immune response, which is crucial for defending against many pathogens that enter through mucosal surfaces.
10. Potential for Combination Vaccines: Nanoparticles can encapsulate multiple antigens, enabling the development of combination vaccines that protect against several diseases simultaneously.
11. Improved Immunogenicity: Nanoparticles can enhance the presentation of antigens to dendritic cells and other immune cells, leading to a stronger and more robust immune response.

12. Reduction in Cold Chain Requirements: Many nanoparticle formulations can be designed to remain stable at room temperature, reducing the logistical challenges associated with cold chain storage and transport.
13. Boosted Cellular Responses: Topical vaccines can stimulate both humoral (antibody-mediated) and cellular (T cell-mediated) immune responses, providing a comprehensive defense against pathogens.
14. Increased Patient Acceptance: The less invasive nature of topical vaccinations may lead to greater acceptance among individuals hesitant to receive traditional injections, particularly in populations such as children.
15. Rapid Onset of Immune Response: The skin's rich supply of immune cells can lead to a quicker immune response compared to traditional methods, potentially offering faster protection against infectious diseases.
16. Minimal Equipment Requirement: Topical vaccination typically requires less specialized equipment than injections, making it more accessible in resource-limited settings.
17. Environmental Benefits: By reducing the reliance on syringes and needles, topical vaccines may decrease medical waste and the associated environmental impact.
18. Innovative Delivery Systems: The use of nanoparticles allows for the exploration of various innovative delivery systems, such as microneedle patches, which can further enhance patient comfort and compliance.
19. Reduced Need for Professional Healthcare Settings: Topical vaccines can potentially be administered outside traditional healthcare settings, making vaccination more accessible, especially in rural or underserved areas.

Immunization strategies for nanoparticles base topical vaccination:-

Vaccination strategies for nanoparticle-based local immunization focus on optimizing vaccine delivery, enhancing immune responses, and ensuring patient compliance through innovative approaches. To begin with, the choice and composition of nanoparticles play an important role in the effectiveness of a vaccination strategy. Various types of nanoparticles, such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles, can be used based on their ability to effectively encapsulate antigens. Modification of the surface of these nanoparticles with ligands or adjuvants can further improve their stability and enhance their uptake by immune cells, promoting a stronger immune response.

Another important aspect of vaccination strategies is the process of antigen loading. Optimizing the encapsulation efficiency of antigens in nanoparticles ensures that an adequate dose is delivered. In addition, designing nanoparticles for controlled or sustained release of antigen can enhance immune recognition and prolong the immune response, making vaccination more effective. Administration techniques also play an important role in the success of nanoparticle-based topical vaccinations. The use of microneedle patches offers a promising solution by facilitating painless delivery of nanoparticles through the skin. This approach not only increases access and uptake but also improves patient compliance. Alternatively, formulating nanoparticles into gels or creams allows for easier topical application, further increasing acceptance among potential vaccine recipients.

Incorporation of adjuvants into nanoparticle formulations can significantly enhance the immune response. By incorporating substances that promote local inflammation and recruit immune cells to the site of vaccination, nanoparticles can act as carriers and immune enhancers. This dual action is particularly beneficial, as it increases the overall immunity of the vaccine. Targeting immune cells is another strategy that can significantly improve vaccination outcomes. Engineering nanoparticles to specifically interact with receptors on immune cells, such as dendritic cells, can enhance uptake and presentation of antigens. Developing biomimetic nanoparticles that mimic pathogens or immune cells could also improve interactions with the immune system, leading to stronger responses. Formulation optimization is essential to ensure stability and efficacy of nanoparticle vaccines.

It is important to create formulations that remain stable during storage and transportation, retaining their effectiveness until administration. It is also necessary to ensure that the nanoparticles are stable under different pH and temperature conditions for the success of vaccination. Determining the optimal dose of nanoparticles is an essential part of vaccination strategy. Preclinical studies can help identify the most effective dose that elicits a robust immune response without adverse effects. In addition, exploring fractionated dosing strategies can

gradually increase the immune response, minimizing side effects while maximizing protection. Monitoring the immune response after vaccination is important to assess the efficacy of nanoparticle-based vaccines.

Identifying and tracking biomarkers that indicate immune activation, such as antibody levels and T-cell activation, can provide insight into vaccine efficacy. Longitudinal studies are also valuable to assess the duration of immune protection provided by these innovative vaccines. Combinations of nanoparticle vaccines with other vaccination strategies may provide additional benefits. Co-administration of nanoparticle vaccines with conventional injectable vaccines can enhance overall immunity against many pathogens. In addition, the development of multivalent vaccines containing multiple antigens from different pathogens may broaden the protection afforded to individuals. Finally, regulatory and safety considerations are paramount in the development of nanoparticle-based topical vaccines.

A thorough safety assessment is essential to ensure that the formulations are non-toxic and well tolerated. Adherence to regulatory guidelines throughout the vaccine development process, including preclinical and clinical trials, ensures that vaccines are safe and effective for public use.

Limitation of Nanoparticles based topical vaccination:-

1. Skin Penetration: Difficulty in penetrating the skin's protective barrier (stratum corneum).
2. Immune Response Variability: Individual differences in skin structure and immune responses can lead to inconsistent vaccine efficacy.
3. Stability and Storage: Sensitivity to environmental conditions affects stability during storage and transport.
4. Dosing Challenges: Variability in skin thickness and absorption complicates dosage determination.
5. Potential for Toxicity: Some nanoparticles may be cytotoxic or cause unwanted inflammatory responses.
6. Regulatory Hurdles: Complex regulatory requirements can delay development and approval.
7. Cost and Manufacturing: High production costs and challenges in achieving consistent manufacturing at scale.
8. Limited Knowledge of Long-term Effects: Insufficient understanding of potential long-term health effects.
9. Technical Challenges in Formulation: Difficulties in creating optimal formulations for stability and immune interaction.
10. Public Perception and Acceptance: Concerns about safety may affect public acceptance and uptake.

I. CONCLUSION

The strategy of utilizing nanoparticles for topical vaccination represents a significant advancement in immunization technology, with the potential to transform the way vaccines are delivered and administered. The unique attributes of nanoparticles—such as their ability to enhance antigen stability, improve skin permeability, and promote localized immune responses—offer distinct advantages over conventional vaccination methods. This approach not only aims to increase vaccine efficacy but also seeks to reduce systemic side effects, making vaccination more acceptable to patients.

While the benefits are substantial, the field faces several critical challenges that must be addressed to fully realize the potential of nanoparticle-based topical vaccines. Overcoming the inherent barriers posed by the skin's structure, ensuring consistent dosing, and addressing safety and toxicity concerns are essential for the successful translation of these technologies into clinical practice. Furthermore, the variability in individual immune responses necessitates a deeper understanding of how different nanoparticle formulations interact with the immune system.

Future research is poised to explore innovative solutions, such as the use of multifunctional nanoparticles, targeted delivery systems, and the integration of nanoparticles with adjuvants to enhance immunogenicity. Additionally, as advancements in nanotechnology continue to progress, the development of smart delivery systems that can respond to physiological cues could further improve the effectiveness of topical vaccines.

The potential applications of nanoparticle-based topical vaccination extend beyond infectious diseases; they could also pave the way for effective vaccination against chronic diseases, such as cancer and allergies. As the global health landscape evolves, there is an urgent need for innovative vaccination strategies that can address emerging pathogens and enhance vaccine uptake, especially in regions with limited healthcare infrastructure.

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