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Contemporary Developments in Science and Technology

Volume II

Editors:
Dr. Vishnu Prabhakar Srivastava
Dr. Shailendra B. Kolhe
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PREFACE

The rapidly evolving landscape of science and technology continues to redefine the way we perceive, interact with, and improve the world around us. The present book, Contemporary Developments in Science and Technology, is a compilation of cutting-edge research, critical reviews, and innovative perspectives that reflect the dynamic progress occurring across various scientific and technological domains. It aims to serve as a valuable resource for academicians, researchers, industry professionals, and students who seek to understand the current trends and future directions shaping the modern scientific world.

This volume brings together multidisciplinary contributions that span fields such as physical sciences, life sciences, information technology, environmental science, biotechnology, materials science, and engineering. The chapters not only highlight theoretical advancements but also emphasize practical applications and the societal impacts of these emerging technologies. Special attention is given to sustainable innovation, digital transformation, and the ethical implications of scientific progress.

The book underscores the importance of an integrated approach in solving contemporary challenges—be it climate change, public health, food security, or energy efficiency—through the fusion of scientific knowledge and technological innovation. Each contribution has been carefully selected and peer-reviewed to ensure academic rigor, relevance, and clarity. The diversity of topics and authors reflects a collaborative spirit and a shared commitment to fostering knowledge dissemination and interdisciplinary dialogue.

We believe that Contemporary Developments in Science and Technology will inspire readers to explore new ideas, engage in meaningful research, and contribute actively to the advancement of their respective fields. As we navigate an era marked by both unprecedented innovation and complex global challenges, the role of science and technology in driving positive change is more crucial than ever.

We extend our sincere gratitude to all contributors, reviewers, and supporting institutions whose efforts have made this publication possible. It is our hope that this book becomes a useful guide and a catalyst for further exploration in the fascinating journey of scientific and technological progress.

- Editors

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TECHNOLOGIES FOR THE MANUFACTURING OF LIPID-BASED NANOCARRIERS

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Abstract:

Lipid-based nanocarriers have emerged as a versatile and efficient platform for drug delivery, owing to their biocompatibility, ability to encapsulate both hydrophilic and hydrophobic agents, and capacity for targeted delivery. This chapter provides a comprehensive overview of the various technologies employed in the manufacturing of lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid–polymer hybrid nanoparticles. Key methods such as high-pressure homogenization, solvent emulsification-evaporation, microfluidics, ultrasonication, and supercritical fluid technology are discussed with a focus on their principles, advantages, limitations, and scalability for industrial production. Emerging techniques and innovations aimed at improving reproducibility, particle size control, and drug loading efficiency are also highlighted. The chapter further examines the role of process parameters, equipment design, and formulation strategies in optimizing nanocarrier performance for pharmaceutical and biomedical applications.

Keywords: Lipid-Based Nanocarriers, Efficient Drug Delivery, Emerging Approaches, Large Scale Manufacturing Technology

Introduction:

Lipid-based nanocarriers are advanced drug delivery systems composed mainly of biocompatible and biodegradable lipids designed to transport therapeutic agents at the nanoscale. They are especially effective in improving the solubility, stability, and bioavailability of poorly water-soluble drugs. These systems include various types such as liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid–polymer hybrid nanoparticles. Their ability to encapsulate both hydrophilic and lipophilic drugs makes them highly versatile for a wide range of applications. One of their key advantages is the potential for targeted delivery and controlled drug release, which enhances treatment efficacy while reducing side effects. The lipid composition of these nanocarriers mimics biological membranes, promoting better biocompatibility and cellular uptake. Liposomes, made of phospholipid bilayers, have been extensively used for delivering anticancer and antimicrobial agents. SLNs and NLCs offer improved stability, scalability, and drug loading capacity over traditional liposomes. The production of these carriers involves various techniques including high-pressure

homogenization, ultrasonication, solvent evaporation, and microfluidics. As a result, lipid-based nanocarriers are gaining increasing attention in pharmaceutical, cosmetic, and nutraceutical fields for their potential to revolutionize drug delivery and therapeutic outcomes[1,2].

Lipid-based nanocarriers play a crucial role in drug delivery and biomedical applications due to their ability to enhance the therapeutic effectiveness of drugs while minimizing adverse effects. Their biocompatibility and structural similarity to biological membranes enable efficient drug encapsulation, protection, and targeted delivery, particularly for drugs with poor water solubility or low bioavailability. These carriers facilitate controlled and sustained drug release, improving patient compliance and reducing dosing frequency. In cancer therapy, they enable site-specific delivery of chemotherapeutic agents, thereby reducing systemic toxicity. Additionally, lipid-based nanocarriers are employed in gene delivery, vaccine development, and imaging, offering multifunctionality in diagnostics and therapeutics. Their tunable surface properties also allow for the attachment of ligands, enabling active targeting of specific tissues or cells. The adaptability of these nanocarriers makes them suitable for treating a variety of diseases, including infections, neurological disorders, and cardiovascular conditions. Furthermore, their scalable production and ability to incorporate both small molecules and macromolecules have accelerated their translation from research to clinical use. Overall, lipid-based nanocarriers represent a transformative technology in modern medicine, offering safer, more effective, and personalized therapeutic options[3].

Types of Lipid-Based Nanocarriers

1. **Liposomes**: Spherical vesicles composed of one or more phospholipid bilayers, capable of carrying both hydrophilic and lipophilic drugs. They are widely used due to their biocompatibility and ability to encapsulate a variety of therapeutic agents.
2. **Solid Lipid Nanoparticles (SLNs)**: Made from solid lipids that remain solid at room and body temperatures, SLNs offer high physical stability, controlled drug release, and protection of sensitive drugs.
3. **Nanostructured Lipid Carriers (NLCs)**: These are second-generation lipid nanoparticles combining solid and liquid lipids. NLCs improve drug loading capacity and prevent drug leakage during storage.
4. **Lipid–Polymer Hybrid Nanoparticles**: These combine the structural benefits of polymers with the biocompatibility of lipids. They are suitable for delivering nucleic acids, peptides, and other complex molecules.
5. **Self-Emulsifying Drug Delivery Systems (SEDDS)**: Isotropic mixtures of oils, surfactants, and solvents that form emulsions in the gastrointestinal tract, enhancing the oral bioavailability of poorly soluble drugs.
6. **Ethosomes**: Lipid vesicles with high ethanol content that enhance skin permeability, making them useful for transdermal and dermal drug delivery.

7. **Transfersomes**: Ultra-deformable liposomes designed for enhanced skin penetration and delivery of large molecules through the skin.
8. **Cubosomes**: Nanostructured particles with a cubic crystalline structure, offering high drug-loading capacity and sustained release.

These diverse types of lipid-based nanocarriers enable tailored solutions for specific therapeutic needs, ranging from oral to transdermal and intravenous drug delivery[4].

Manufacturing Technologies

1. High-Pressure Homogenization (HPH)

High-Pressure Homogenization (HPH) is one of the most widely used and scalable techniques for the production of lipid-based nanocarriers, particularly solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs**)**. This method involves forcing a lipid dispersion through a narrow gap (homogenization valve) at extremely high pressures—typically ranging from 100 to 2000 bar. The intense shear forces, turbulence, and cavitation generated during this process break down large lipid droplets into nanosized particles[5,6].

There are two main variants of HPH:

- **Hot Homogenization**: The lipid is melted above its melting point, and the drug is dissolved or dispersed in it. This lipid melt is then emulsified in a hot aqueous surfactant solution and subjected to high-pressure homogenization. This method is suitable for **lipophilic drugs** and ensures the lipid remains in the liquid state during processing.
- **Cold Homogenization**: The drug-loaded lipid is solidified (typically using liquid nitrogen or dry ice), ground into microparticles, and then dispersed in a cold aqueous phase before homogenization. This approach is preferred for thermolabile or hydrophilic drugs**,** as it minimizes exposure to heat.

Advantages:

- **Solvent-free** production, making it environmentally friendly and suitable for pharmaceuticals.
- **Scalability** from laboratory to industrial scale.
- Production of **physically stable** nanosuspensions with narrow particle size distribution.

Limitations:

- Potential degradation of heat-sensitive compounds during hot homogenization.
- High energy input and equipment cost.
- Risk of metal contamination due to mechanical stress on equipment components.

Overall, HPH is a robust and efficient method for the production of lipid-based nanocarriers, offering consistent particle size control, good reproducibility, and compatibility with large-scale pharmaceutical manufacturing.

2. Ultrasonication (Probe or Bath Sonication)

Ultrasonication is a commonly used method for the preparation of lipid-based nanocarriers such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). This technique utilizes high-frequency sound waves (usually in the range of 20 kHz to several MHz) to break down lipid aggregates into smaller, nanometer-sized particles through acoustic cavitation—the formation, growth, and implosive collapse of microscopic bubbles in a liquid.

There are two main types of ultrasonication[7,8]:

- **Probe Sonication**: A metal probe is directly immersed into the formulation, delivering intense, localized energy. It is highly effective for reducing particle size and producing nanoparticles with narrow size distribution. However, it may generate significant heat and metal contamination, which could degrade sensitive drugs.
- **Bath Sonication**: The formulation is placed in a sealed container and immersed in a sonication bath filled with water. It provides gentler, uniform energy distribution and is suitable for delicate formulations, but is less efficient than probe sonication in particle size reduction.

Advantages:

- Simplicity and low cost, making it ideal for laboratory-scale production.
- Ability to produce uniformly sized nanoparticles.
- Effective for encapsulating both hydrophilic and lipophilic drugs in various lipid matrices.

Limitations:

- Poor scalability for large-scale manufacturing.
- Generation of heat, which may degrade heat-sensitive drugs or lipids.
- Metal particle shedding from the sonication probe if not properly maintained.
- Limited control over particle size compared to more advanced methods like high-pressure homogenization.

Ultrasonication is often used in combination with other techniques (e.g., thin-film hydration) to enhance nanoparticle formation. While it is more suited for research and small-batch formulations, it remains a valuable tool in the early development of lipid-based nanocarrier systems.

3. Solvent emulsification–evaporation method

The solvent emulsification–evaporation method is a widely used technique for preparing lipid-based nanocarriers, especially solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoparticles encapsulating lipophilic drugs. This method involves the dissolution of lipids and drug(s) in a water-immiscible organic solvent, followed by

emulsification into an aqueous phase containing surfactants, and subsequent removal of the organic solvent through evaporation[9].

Steps Involved:

1. Lipid and drug dissolution: Lipids and lipophilic drugs are dissolved in an organic solvent such as chloroform, dichloromethane, or ethyl acetate.
2. Emulsification: The organic phase is emulsified into an aqueous phase (containing surfactants or stabilizers) under high-speed stirring or sonication, forming an oil-in-water (O/W) emulsion.
3. Solvent evaporation: The organic solvent is removed by continuous stirring at atmospheric or reduced pressure, leading to precipitation of the lipid phase into nanoparticles as the solvent evaporates.
4. Nanoparticle formation: Lipid nanocarriers are formed as the lipid droplets solidify upon solvent removal, with the drug encapsulated inside.

Advantages:

- Suitable for lipophilic drugs with poor water solubility.
- Simple and effective for small- to medium-scale production.
- Allows relatively good control over particle size and drug loading.
- Does not require high temperatures, making it suitable for thermosensitive compounds.

Limitations:

- Use of toxic organic solvents, which must be completely removed for pharmaceutical applications.
- Low encapsulation efficiency for hydrophilic drugs.
- Residual solvent traces can pose safety concerns and require additional purification.
- Not easily scalable for industrial production compared to solvent-free methods like high-pressure homogenization.

This method is particularly useful in the early development phase of lipid-based formulations, offering a balance between formulation versatility and ease of preparation. However, for regulatory compliance and large-scale manufacturing, solvent removal and environmental concerns must be carefully addressed

4. Solvent Injection (Ethanol Injection or Phase Inversion)

The solvent injection method, also known as ethanol injection or phase inversion, is a simple and effective technique for producing lipid-based nanocarriers such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). It involves dissolving lipids in a water-miscible organic solvent (commonly ethanol or acetone) and injecting this solution into an aqueous phase under constant stirring.

Process Overview:

1. Lipid dissolution: Lipids (with or without the drug) are dissolved in a water-miscible solvent like ethanol.
2. Injection: The organic phase is rapidly injected or added dropwise into an aqueous phase (containing surfactants or stabilizers) under continuous stirring.
3. Nanoparticle formation: The lipid precipitates immediately upon contact with water, forming nanoparticles due to solvent diffusion and lipid self-assembly.
4. Solvent removal: The residual solvent is removed by evaporation under reduced pressure or vacuum filtration.

Advantages:

- Simple, fast, and reproducible, ideal for small-scale or laboratory use.
- No requirement for high temperatures, making it suitable for heat-sensitive (thermolabile) drugs.
- Low energy input compared to high-pressure methods.
- Avoids the use of toxic, water-immiscible solvents (e.g., chloroform), improving safety.

Limitations:

- Residual solvent (e.g., ethanol) must be removed completely to meet regulatory standards.
- Often results in larger particle sizes and broad size distributions compared to other methods.
- Less efficient for encapsulating hydrophilic drugs.
- Scalability can be challenging without precise control of mixing parameters.

This method is especially useful for formulating lipid-based nanocarriers in early-stage research or where gentle processing is required. It is also considered more environmentally friendly than traditional solvent evaporation methods, although further process optimization is often needed for commercial-scale applications.

5. **Microfluidization**

Microfluidization is a high-shear, high-energy method used to produce lipid-based nanocarriers such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) with uniform particle size and narrow size distribution. This technique uses a device called a microfluidizer, which forces the formulation through microchannels under high pressure, leading to particle size reduction by shear stress, cavitation, and impact[10,11].

Process Overview:

1. **Pre-emulsion preparation**: The lipid and drug are first mixed to form a coarse emulsion, typically by high-speed stirring or sonication.
2. **Microfluidization**: The emulsion is passed through a microfluidizer at high pressure (typically 500–30,000 psi), where it is forced through narrow micro-channels.

3. **Particle size reduction**: Within these channels, the mixture is subjected to extreme shear forces and turbulence, breaking down the droplets into uniform nanoscale particles.
4. **Recirculation**: The process may be repeated multiple times (passes) to achieve the desired particle size and distribution.

Advantages:

- Produces uniform, stable nanoparticles with narrow size distribution.
- Highly reproducible and suitable for scaling up to industrial production.
- Capable of processing large volumes continuously.
- Works well with both hydrophilic and lipophilic drugs.
- Ideal for formulations requiring sterility, as it can be operated in closed systems.

Limitations:

- Requires expensive equipment and maintenance.
- High-pressure operation may degrade sensitive drugs or biomolecules.
- Thermal rise during processing may necessitate cooling to protect heat-labile compounds.
- Not ideal for formulations with very high viscosity, which can clog the microchannels.

Microfluidization is increasingly used in the pharmaceutical industry due to its precision, scalability, and suitability for Good Manufacturing Practice (GMP) settings. It is particularly advantageous for applications where consistent nanoparticle size and batch-to-batch uniformity are critical, such as in vaccine delivery, cancer therapy, and injectable drug formulations.

6. Supercritical Fluid Technology

Supercritical Fluid (SCF) technology is an advanced, eco-friendly method used to prepare lipid-based nanocarriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes. This technique utilizes supercritical fluids, primarily supercritical carbon dioxide ($scCO_2$), as solvents or antisolvents to facilitate the formation of nanoparticles under specific conditions of temperature and pressure[12,13].

Key Methods in SCF Technology:

1. **Rapid Expansion of Supercritical Solutions (RESS):**
   - Lipids are dissolved in $scCO_2$, and the solution is rapidly expanded through a nozzle into a low-pressure chamber.
   - This sudden pressure drop causes supersaturation and precipitation of lipid nanoparticles.
2. **Supercritical Anti-Solvent (SAS) Process:**
   - The drug and lipid are first dissolved in an organic solvent.
   - $scCO_2$ is introduced as an **antisolvent**, which reduces the solubility of the solute, leading to precipitation of nanoparticles.
3. **Particles from Gas-Saturated Solutions (PGSS):**
   - Lipids are melted and saturated with $scCO_2$.

- The mixture is expanded through a nozzle, forming fine particles as the gas escapes.

Advantages:

- Green and solvent-free (or low solvent) technique, reducing environmental and toxicological concerns.
- Mild operating temperatures, ideal for thermolabile or sensitive drugs.
- Produces solvent-free, high-purity nanoparticles.
- Tunable process parameters allow control over particle size, morphology, and drug loading.
- Avoids the use of toxic organic solvents used in conventional emulsification methods.

Limitations:

- Requires specialized, high-cost equipment and technical expertise.
- Limited solubility of many lipids and drugs in $scCO_2$.
- Process optimization can be complex and time-consuming.
- Scalability is still under development for certain formulations.

Supercritical fluid technology holds great promise for producing high-quality, stable lipid-based nanocarriers, especially for parenteral and pulmonary drug delivery. As a clean, scalable, and solvent-minimizing method, it aligns well with current pharmaceutical industry trends toward green manufacturing and regulatory compliance.

7. Double Emulsion Method (W/O/W or O/W/O):

The double emulsion method is a specialized technique used to formulate lipid-based nanocarriers—especially for the encapsulation of hydrophilic drugs, proteins, peptides, and nucleic acids. It involves the formation of a multiple emulsion system, typically either water-in-oil-in-water (W/O/W) or oil-in-water-in-oil (O/W/O), depending on the solubility of the drug and the desired delivery system[14].

Process Overview (W/O/W Emulsion - Commonly Used):

1. **Primary Emulsion (W/O)**: A solution of the hydrophilic drug in water (internal aqueous phase) is emulsified into a lipid-containing organic phase (oil) using high-speed stirring or sonication.
2. **Secondary Emulsion (W/O/W)**: The primary W/O emulsion is then further emulsified into an external aqueous phase containing surfactants or stabilizers to form a W/O/W system.
3. **Solvent Removal and Solidification**: The organic solvent is evaporated or extracted, causing the lipid to solidify and form nanoparticles that entrap the drug in the internal aqueous phase.

Advantages:

- Highly effective for encapsulating hydrophilic bioactives like proteins and nucleic acids.
- Suitable for controlled or sustained drug release.
- Allows co-encapsulation of both hydrophilic and lipophilic drugs in separate phases.
- Protects sensitive drugs from degradation by isolating them within inner compartments.

Limitations:

- Often results in low encapsulation efficiency and drug leakage, especially during solvent removal.
- Requires careful surfactant selection and optimization to maintain emulsion stability.
- Scaling up is challenging due to complexity and instability of the emulsion system.
- Residual organic solvents may need to be completely removed to ensure safety and compliance.

The double emulsion method is widely used in vaccine delivery, gene therapy, and protein-based drug formulations, where protection and controlled release of sensitive therapeutic agents are crucial. Despite its limitations, it remains a powerful tool for developing sophisticated lipid-based nanocarrier systems in biomedical applications.

8. Thin-Film Hydration Method (Bangham Method)

The Thin-Film Hydration Method, also known as the Bangham Method, is one of the most established and widely used techniques for preparing liposomes, a key class of lipid-based nanocarriers. It is particularly suited for encapsulating both hydrophilic and lipophilic drugs within the aqueous core or lipid bilayer, respectively[15,16].

Process Overview:

1. **Lipid Dissolution**: Lipids (such as phospholipids and cholesterol) are dissolved in an organic solvent or a mixture of solvents like **chloroform**, **methanol**, or **ethanol**.
2. **Film Formation**: The solvent is evaporated under reduced pressure using a **rotary evaporator**, forming a **thin lipid film** on the inner surface of a round-bottom flask.
3. **Hydration**: The dry film is hydrated with an aqueous solution (containing the hydrophilic drug if applicable), leading to **swelling and peeling off** of the lipid layers to form **multilamellar vesicles (MLVs)**.
4. **Size Reduction**: The liposomes may then be sonicated or extruded through polycarbonate membranes to reduce particle size and convert MLVs into **small unilamellar vesicles (SUVs)** or **large unilamellar vesicles (LUVs)**.

Advantages:

- **Simple and cost-effective** method suitable for lab-scale formulation.
- Allows encapsulation of both **hydrophilic and lipophilic molecules**.
- Useful for producing **biocompatible and customizable liposomes**.
- Facilitates incorporation of **functional lipids or targeting ligands**.

Limitations:

- **Low encapsulation efficiency**, especially for hydrophilic drugs.
- **Batch-to-batch variability** due to manual steps.
- Residual solvent may remain in the final product if not thoroughly removed.
- Not easily scalable for industrial production.
- Requires additional processing (e.g., sonication, extrusion) for uniform size distribution.

This ethodm laid the foundation for liposomal drug delivery systems and continues to be widely used in academic research and preclinical studies. It provides a robust and adaptable platform for developing lipid-based nanocarriers, especially when formulation flexibility and drug compatibility are key considerations.

9. Microfluidics

Microfluidics is an advanced and highly precise method for the production of lipid-based nanocarriers, especially liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid–polymer hybrid nanoparticles. This technique involves the manipulation of fluids within microchannels (typically 10–100 micrometers in diameter), allowing controlled mixing and self-assembly of lipid nanoparticles at the nanoscale[17,18].

Process Overview:

1. **Fluid Preparation**: Lipids (and drug, if lipophilic) are dissolved in a water-miscible organic solvent such as ethanol, while the aqueous phase contains hydrophilic drug or stabilizers.
2. **Controlled Mixing**: The two phases are introduced into the microfluidic device using precision pumps. The mixing occurs at a **precisely controlled flow rate and ratio** inside a micromixer.
3. **Self-Assembly**: As the organic and aqueous phases meet, rapid mixing causes supersaturation of lipids, leading to **spontaneous self-assembly** into nanoparticles.
4. **Collection and Purification**: The resulting nanoparticle suspension is collected and may undergo dialysis or filtration to remove residual solvent.

Advantages:

- Produces **uniform nanoparticles** with tight size distribution and tunable properties.
- Highly **reproducible** and suitable for **continuous manufacturing**.
- Operates under **mild conditions**, protecting sensitive biomolecules.
- Minimal use of solvents and reagents, making it **eco-friendly**.
- Allows **precise control** over particle size, structure, and composition by adjusting flow parameters.

Limitations:

- **High initial cost** for device fabrication and instrumentation.

- **Low throughput** limits its use for large-scale production (though parallelization is being developed).
- May require optimization for **different lipid and drug types**.
- **Potential clogging** of channels with high-viscosity or particulate-laden solutions.

Microfluidics is a cutting-edge platform well-suited for personalized medicine, RNA delivery, vaccines, and targeted therapeutics, where precise control and batch consistency are critical. Its scalability and integration with automation make it a promising technology for the future of nano-pharmaceutical manufacturing.

10. Spray Drying

Spray drying is a widely used technique to convert lipid-based nanocarrier suspensions—such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes—into dry, free-flowing powders. This process enhances the stability, shelf-life, and ease of handling of nanocarriers, making it especially useful for oral, pulmonary, or topical drug delivery systems[19,20].

Process Overview:

1. **Preparation of Suspension**: The lipid-based nanocarriers are first prepared in aqueous suspension using conventional methods (e.g., high-pressure homogenization, ultrasonication).
2. **Addition of Drying Aids**: Excipients like **carbohydrates (e.g., mannitol, lactose)** or **polymers (e.g., PVA, PEG)** are added as drying aids or protectants to prevent aggregation and maintain particle integrity during drying.
3. **Atomization**: The suspension is pumped into a **spray dryer** and atomized using a nozzle or rotary atomizer, forming fine droplets.
4. **Drying**: The droplets are exposed to **hot air** (inlet temperatures typically between 100–200 °C), which causes **rapid evaporation** of water and solidification of the particles.
5. **Collection**: The dried particles are collected as a fine powder using a cyclone separator or filter system.

Advantages:

- Scalable and cost-effective method suitable for industrial production.
- Converts liquid nanocarrier formulations into stable solid dosage forms.
- Enables controlled particle size, useful for inhalable or oral delivery.
- Compatible with various excipients to optimize stability and performance.

Limitations:

- Exposure to high temperatures may degrade heat-sensitive drugs or lipids.
- Particle aggregation or loss of nanostructure can occur without proper formulation.
- Residual moisture content may affect powder flow and stability if not optimized.

Spray drying offers a practical and efficient approach for transforming lipid-based nanocarriers into stable dry formulations. It is increasingly applied in drug delivery, especially for inhalable nanomedicines, oral tablets or capsules, and transdermal products, where product stability and patient convenience are essential.

Scale-Up Considerations

The transition from laboratory-scale to industrial-scale manufacturing of lipid-based nanocarriers (such as liposomes, solid lipid nanoparticles [SLNs], and nanostructured lipid carriers [NLCs]) presents several technical, economic, and regulatory challenges[21,22]:

1. Scale-Up of Production Methods: Techniques like thin-film hydration and ultrasonication, though effective at small scales, are often difficult to scale up due to poor batch uniformity and high energy demands.
2. Particle Size Control: Achieving consistent and narrow particle size distribution is more challenging at larger volumes, which can affect drug release, bioavailability, and therapeutic outcomes.
3. Encapsulation Efficiency and Stability: Maintaining high drug loading and preventing drug leakage or degradation during production, storage, and transportation are difficult at scale.
4. Sterilization and Contamination Control: Lipid-based nanocarriers are sensitive to heat, making terminal sterilization difficult. Ensuring aseptic conditions is critical but costly and complex.
5. Equipment and Process Cost: High-end equipment like microfluidizers, high-pressure homogenizers, or freeze dryers involve significant capital investment and maintenance costs.
6. Batch-to-Batch Consistency: Reproducibility of physicochemical properties (size, zeta potential, drug loading) is often a challenge, affecting quality control and regulatory compliance.
7. Scalability of Raw Materials: Lipids, surfactants, and stabilizers used at lab scale may not always be available in pharmaceutical-grade quality or bulk quantities, limiting scale-up.
8. Long-Term Stability and Shelf-Life: Ensuring that nanoparticles remain stable (without aggregation, oxidation, or drug leakage) over long periods, especially in dry or reconstituted forms, remains a key challenge.
9. Regulatory and Quality Assurance Barriers: Regulatory guidelines for nanomedicines are still evolving. Comprehensive characterization, toxicity testing, and compliance with GMP standards are stringent and resource-intensive.
10. Formulation Complexity: Developing a scalable formulation that balances biocompatibility, therapeutic efficiency, and manufacturability often requires multiple rounds of optimization.

Overcoming these challenges requires interdisciplinary collaboration, technological innovation, and adherence to regulatory best practices. Advances in continuous manufacturing, automation, and novel drying techniques are promising directions for enabling the successful commercial translation of lipid-based nanocarrier systems.

Future Trends

The manufacturing of lipid-based nanocarriers has evolved significantly, with recent innovations aimed at enhancing scalability, reproducibility, drug loading, and targeting efficiency. These advances are bridging the gap between laboratory-scale success and industrial-scale application, while also meeting the demands of precision medicine and emerging therapies[23,24].

1. **Artificial Intelligence (AI) and Machine Learning (ML)**
   - AI-based modeling for **formulation prediction**, optimization, and process control.
   - Enhances efficiency in **design of experiments (DoE)** and reduces development time.
2. **3D Printing and Personalized Nanomedicine**
   - Incorporation of lipid nanocarriers into 3D-printed drug delivery systems for personalized therapy.
3. **Green Nanotechnology**
   - Focus on sustainable solvents, biodegradable lipids, and energy-efficient processes.
   - Development of zero-waste nanomanufacturing protocols.
4. **Modular and Portable Manufacturing Units**
   - On-demand, point-of-care production platforms for vaccines and biologics, especially useful in remote or resource-limited settings.
5. **Regulatory Harmonization and Standards**
   - Development of global regulatory frameworks and standardized testing protocols to accelerate clinical translation and approval.

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MESOPOROUS SILICA NANOPARTICLES: A PROMISING CARRIER FOR TARGETED DRUG DELIVERY

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Abstract:

Mesoporous silica nanoparticles (MSNs) have gained significant attention as advanced drug delivery vehicles due to their highly ordered porous structure, large surface area, tunable pore size, and ease of surface functionalization. These characteristics make MSNs ideal candidates for encapsulating a wide range of therapeutic agents and enabling controlled, sustained, and stimuli-responsive drug release. This chapter explores the design, synthesis, and modification strategies of MSNs that enhance their performance as targeted drug delivery carriers. It discusses various functionalization techniques that enable specific targeting to diseased tissues or cells, thereby minimizing systemic side effects and improving therapeutic outcomes. The chapter also reviews recent advances in MSN-based delivery systems for cancer therapy, gene delivery, and other biomedical applications. Finally, the chapter addresses challenges related to biocompatibility, toxicity, and clinical translation, offering insights into the future potential of MSNs in personalized and precision medicine. Through a comprehensive analysis, this chapter underscores the pivotal role of MSNs in the evolving landscape of nanomedicine and targeted therapeutics.

Keywords: Nanotechnology, Mesoporous Silica Nanoparticles, Targeted Drug Delivery, Enhanced Therapeutic Potential

Introduction:

Nanocarriers have revolutionized the field of drug delivery by enabling more efficient, controlled, and targeted transport of therapeutic agents. These nanoscale systems can encapsulate drugs, protect them from degradation, and improve their solubility and bioavailability. Conventional drug delivery often suffers from systemic toxicity and poor site-specificity, which nanocarriers aim to overcome. A wide range of nanocarrier systems have been developed, including liposomes, dendrimers, polymeric nanoparticles, and inorganic materials. Among these, inorganic nanocarriers like mesoporous silica nanoparticles (MSNs) offer unique advantages due to their structural stability and tunable pore characteristics. Nanocarriers can be engineered for passive targeting, taking advantage of the enhanced permeability and retention (EPR) effect in tumours. They can also be modified for active targeting by attaching ligands that

bind to specific cellular receptors. Moreover, stimuli-responsive nanocarriers can release drugs in response to internal or external triggers such as pH, temperature, or light. These advancements aim to improve therapeutic efficacy while minimizing off-target effects and toxicity. As a result, nanocarriers represent a promising strategy in the development of next-generation drug delivery systems for a variety of diseases [1,2].

Mesoporous silica nanoparticles (MSNs) have emerged as a highly versatile and effective platform in nanomedicine, particularly in targeted drug delivery. First developed in the 1990s through the Mobil Composition of Matter (MCM) synthesis approach, MSNs were initially recognized for their high surface area and ordered pore structures. These properties quickly caught the attention of researchers exploring applications in catalysis, adsorption, and, later, biomedicine. Their structural features—such as small pore sizes (typically 2–50 nm), large pore volume, and high thermal and mechanical stability—make MSNs ideal for loading and releasing therapeutic agents. Compared to organic nanocarriers, MSNs offer greater structural robustness and chemical stability under physiological conditions. Their surface chemistry can be easily modified with functional groups to enable targeted delivery and responsive behaviour. The ability to tailor particle size, shape, and surface properties allows for optimized cellular uptake and biodistribution. In recent years, MSNs have been designed to respond to internal stimuli such as pH, redox gradients, and enzymes, or to external stimuli like light, heat, or magnetic fields. These responsive systems enhance site-specific drug release and reduce systemic toxicity. Researchers have also explored MSNs for co-delivery of multiple therapeutic agents, including drugs, genes, and imaging agents, making them suitable for theranostic applications. Their relatively low toxicity and biodegradability have further boosted their appeal in clinical research. MSNs have shown promising results in the treatment of various diseases, particularly cancers, by enabling precise targeting of tumour tissues. Advances in synthesis techniques, such as soft and hard templating, have improved the uniformity and scalability of MSN production. Surface PEGylation and the attachment of targeting ligands have extended their circulation time and targeting accuracy. Moreover, the porous structure of MSNs protects sensitive drugs from premature degradation in the bloodstream. The internal cavities can be engineered to hold large drug payloads and release them in a controlled manner. With increasing interdisciplinary collaboration, MSNs are now being tested in preclinical models for a variety of applications. Although challenges remain, particularly in regulatory approval and large-scale manufacturing, MSNs represent a significant advancement in nanotechnology-based therapeutics. Their emergence has opened new avenues in personalized and precision medicine, where targeted, efficient, and safe drug delivery is of utmost importance [3,4].

Targeted drug delivery is crucial for improving the efficacy of treatments while minimizing side effects. It allows therapeutic agents to accumulate specifically at diseased sites,

such as tumours, reducing damage to healthy tissues. This precision enhances treatment outcomes and patient safety, especially in chronic or aggressive diseases like cancer. Targeted delivery also enables lower drug dosages, decreasing toxicity and improving patient compliance. Overall, it represents a significant advancement in achieving safer, more efficient, and personalized medical therapies [5].

Structure and Properties of Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are a unique class of nanomaterials characterized by their highly ordered pore structures and exceptional physicochemical properties. These nanoparticles typically possess a pore size ranging between 2 to 50 nanometres, classifying them as mesoporous according to IUPAC standards. The pores are arranged in various well-defined geometries, such as hexagonal (e.g., MCM-41), cubic (e.g., MCM-48), or worm-like networks (e.g., SBA-15), depending on the synthesis method and surfactant template used.

One of the most notable features of MSNs is their high surface area, often exceeding 1,000 m^2/g. This large surface area, combined with significant pore volume, allows for high drug loading capacity. The silica framework provides excellent thermal, chemical, and mechanical stability, making MSNs suitable for various biomedical and pharmaceutical applications. MSNs are usually synthesized via sol-gel methods in the presence of surfactant templates, which are later removed to reveal the mesoporous network.

The particle size of MSNs can be finely controlled, usually within the range of 20–200 nm, which is ideal for passive tumour targeting through the enhanced permeability and retention (EPR) effect. The morphology of MSNs can vary (spherical, rod-like, or tubular), but spherical particles are the most commonly used due to their uniformity and favourable cellular uptake. Surface silanol groups (Si–OH) present on MSNs provide active sites for further functionalization, enabling the attachment of drugs, targeting ligands, polymers, or stimuli-responsive gatekeepers.

The surface charge of MSNs is typically negative due to the presence of silanol groups, which contributes to their colloidal stability in aqueous solutions. These surface properties can be altered through salinization or grafting with organic or polymeric moieties to improve biocompatibility, reduce immunogenicity, and prolong systemic circulation. MSNs also demonstrate excellent dispersibility in biological media when properly modified, which enhances their effectiveness in drug delivery systems.

Another key advantage of MSNs is the ability to design stimuli-responsive systems. By integrating responsive materials (e.g., pH-sensitive polymers, redox-sensitive bonds, or enzyme-cleavable linkers), MSNs can be engineered to release their payload in specific physiological

environments, such as acidic tumour tissues or intracellular compartments. This improves therapeutic efficacy while minimizing off-target effects.

Furthermore, the rigid porous structure protects encapsulated drugs from premature degradation and allows for sustained or controlled release over time. The mesopores can also accommodate a wide variety of cargo types, including hydrophilic and hydrophobic drugs, proteins, nucleic acids, and imaging agents. Because of their biocompatibility and modifiability, MSNs are increasingly being used not only for drug delivery but also for diagnostics, gene delivery, and theranostic.

MSNs possess a tunable mesoporous structure, high surface area, excellent stability, and customizable surface chemistry. These attributes make them a highly promising and adaptable platform for a broad range of biomedical applications, particularly in targeted and controlled drug delivery systems [6-8].

Functionalization and Surface Modification

The functionalization and surface modification of mesoporous silica nanoparticles (MSNs) are vital processes that significantly enhance their performance in biomedical applications, especially in targeted drug delivery, diagnostics, and theranostic. These modifications improve the particles' biocompatibility, circulation time, drug release behaviour, and targeting specificity. Functionalization strategies can be broadly categorized into organic, inorganic, biological ligand-based, and stimuli-responsive modifications [9-11].

1. Organic Surface Modifications

Organic modification involves grafting organic functional groups onto the MSN surface, typically via salinization reactions using organ silanes. Common functional groups include:

- Amines (–NH_2): Introduced using APTES for further conjugation with drugs or targeting moieties.
- Carboxyl (–COOH): Used for coupling with amine-containing molecules via amide bond formation.
- Thiol (–SH): Enables thiol-disulphide exchange reactions, often used in redox-responsive systems.
- Hydrophobic groups: Useful for loading hydrophobic drugs or creating amphiphilic delivery systems.

Organic polymers such as polyethylene glycol (PEG) are widely used to create a "stealth" surface that reduces immunogenicity and increases blood circulation time. Other polymers like chitosan, poly(N-isopropylacrylamide) (PNIPAM), and poly (acrylic acid) (PAA) can impart pH or temperature responsiveness.

2. Inorganic Surface Modifications

Inorganic modifications involve coating or doping MSNs with other inorganic materials to impart additional functionality:

- Gold (Au) or silver (Ag) nanoparticles: Useful for photothermal therapy or imaging.
- Iron oxide (Fe_3O_4): Provides magnetic properties for magnetic targeting or MRI contrast.
- Quantum dots: Enable fluorescence imaging and tracking of MSNs.
- Calcium phosphate or zinc oxide: Improves biodegradability and enhances bioactivity for bone-related applications.

These coatings not only enhance MSN functionality but can also influence drug release, biocompatibility, and targeting capabilities.

3. Targeting Ligands for Active Targeting

To achieve active targeting, MSNs can be functionalized with biological ligands that selectively bind to receptors overexpressed on diseased cells (e.g., tumour cells). Common targeting ligands include:

- Antibodies: High specificity and affinity for target antigens (e.g., anti-HER2 for breast cancer).
- Peptides: Small and versatile ligands like RGD peptides that bind integrin receptors on tumour vasculature.
- Aptamers: Synthetic nucleic acid molecules that fold into unique 3D structures for selective binding to cellular targets.
- Small molecules: Such as folic acid, which targets folate receptors frequently overexpressed in cancer cells.

These ligands enable MSNs to home in on target tissues or cells, enhancing therapeutic efficacy and reducing systemic side effects.

4. Stimuli-Responsive Modifications

Stimuli-responsive MSNs are engineered to release their drug payload in response to specific internal or external triggers. These modifications add "intelligence" to the system, allowing for precise spatiotemporal drug delivery.

- pH-Responsive Systems: Utilize acid-labile bonds (e.g., hydrazone, acetal) or polymers that degrade in acidic environments (like tumour tissues or endosomes), triggering drug release.
- Redox-Responsive Systems: Incorporate disulphide bonds that are cleaved in the presence of high intracellular glutathione (GSH) levels, common in cancer cells.

- Enzyme-Responsive Systems: Use peptide linkers or gatekeepers that are cleaved by overexpressed enzymes (e.g., matrix metalloproteinases or cathepsin B) in pathological tissues.
- Temperature-Responsive Systems: Use thermosensitive polymers like PNIPAM that undergo a phase change at physiological or hyperthermic temperatures, enabling drug release upon heating.
- Light/Magnetic Field Responsive: Incorporate photo-cleavable linkers or magnetic nanoparticles for externally triggered release using light or magnetic fields.

These responsive designs enhance control over the timing and location of drug release, improving therapeutic outcomes while minimizing off-target toxicity

Targeting Strategies

Targeting strategies are central to the successful application of mesoporous silica nanoparticles (MSNs) in nanomedicine, particularly for drug delivery and diagnostic purposes. By improving the specificity and efficiency of delivery, targeting strategies reduce systemic toxicity, enhance therapeutic outcomes, and enable precision medicine. The targeting of MSNs can be broadly divided into passive, active, and stimuli-responsive approaches [12-14].

1. Passive Targeting

Passive targeting exploits the natural physiological differences between normal and pathological tissues. The most notable mechanism is the Enhanced Permeability and Retention (EPR) effect, common in tumour tissues.

- Tumours often have leaky vasculature and poor lymphatic drainage, allowing nanoparticles (typically 20–200 nm) to accumulate more in tumour tissues than in healthy ones.
- MSNs can be designed with optimal size and surface properties to exploit this effect for drug accumulation in solid tumours.
- Though non-specific, passive targeting is foundational and often combined with other targeting strategies.

2. Active Targeting

Active targeting involves functionalizing MSNs with molecules that specifically recognize and bind to receptors or antigens overexpressed on target cells.

a. Ligand-Based Targeting

- Antibodies and Antibody Fragments: Bind to specific antigens such as HER2 (breast cancer), EGFR (lung cancer), or CD44 (stem-like cancer cells). Offer high specificity but can be immunogenic and expensive.
- Peptides: Short amino acid sequences (e.g., RGD) target integrin receptors on tumour vasculature. They are less immunogenic and easier to synthesize than antibodies.

- Aptamers: Synthetic oligonucleotides or peptides with high affinity and specificity for molecular targets.Offer advantages like low immunogenicity and high chemical stability.
- Small Molecules: Molecules like folic acid, hyaluronic acid, or galactose target overexpressed folate, CD44, or ASGPR receptors, respectively. These are cost-effective and widely used in cancer and liver-targeting applications.

b. Cell Membrane Coating

- Biomimetic approaches involve cloaking MSNs with natural cell membranes (e.g., red blood cells, platelets, or cancer cell membranes) to enhance biocompatibility, prolong circulation, and achieve homotypic targeting.

3. Stimuli-Responsive Targeting

Stimuli-responsive MSNs are engineered to release their cargo in response to specific internal or external stimuli, often in conjunction with passive or active targeting.

a. Internal Stimuli

- pH-Responsive Systems: Exploit the acidic tumour microenvironment or endo/lysosomal pH (~5–6) to trigger drug release. Achieved using pH-sensitive linkers or polymers.
- Redox-Responsive Systems: Use disulphide bonds that are cleaved in the presence of high intracellular glutathione (GSH) levels, common in cancer cells.
- Enzyme-Responsive Systems: Incorporate peptide linkers or polymer coatings cleaved by enzymes like matrix metalloproteinases (MMPs) or cathepsins, overexpressed in tumour tissues.

b. External Stimuli

- Light-Responsive Systems: Employ photo-cleavable groups or photosensitizers for controlled release upon exposure to UV or near-infrared light.
- Thermo-Responsive Systems: Use thermosensitive materials (e.g., PNIPAM) that undergo structural changes at elevated temperatures to trigger release.
- Magnetic or Ultrasound-Triggered Systems: Integrate magnetic particles or use ultrasound to induce localized heating or mechanical disruption for cargo release.

4. Dual and Multifunctional Targeting

Advanced MSNs often combine multiple targeting mechanisms for enhanced precision:

- Dual Targeting: Combining passive (EPR effect) and active (ligand-based) targeting improves tumour accumulation and cellular uptake.
- Targeting + Stimuli-Responsiveness: Ligand-functionalized MSNs with stimuli-responsive gatekeepers ensure that drug release occurs only within the target cells.
- Theranostic: MSNs equipped with targeting ligands and imaging agents enable real-time monitoring of biodistribution and therapeutic response.

Biomedical Applications

Mesoporous silica nanoparticles (MSNs) have emerged as a versatile and highly tunable platform in nanomedicine. Their unique physicochemical properties—such as high surface area, large pore volume, tunable particle and pore size, chemical stability, and ease of functionalization—make them ideal candidates for a wide array of biomedical applications. Below are the major biomedical uses of MSNs[15]:

1. Targeted Drug Delivery

One of the most prominent applications of MSNs is in targeted drug delivery. Their porous structure allows for high drug loading, and surface functionalization enables site-specific delivery. Drugs can be encapsulated within the pores and released in response to specific stimuli (e.g., pH, redox, enzymes), allowing for controlled and localized treatment—particularly in cancer, inflammation, and infection.

2. Gene Delivery

MSNs serve as effective carriers for gene therapy agents such as DNA, siRNA, and miRNA. Their porous structure protects genetic material from enzymatic degradation, and surface modifications facilitate cellular uptake and endosomal escape. Gene-loaded MSNs have shown promise in cancer treatment, neurodegenerative disorders, and genetic diseases.

3. Cancer Therapy

MSNs are widely used in oncology for both monotherapy and combination therapy. They can co-deliver chemotherapeutic agents, photothermal agents, or genes directly to tumour cells. Functionalization with targeting ligands like folic acid, antibodies, or peptides enables active targeting of tumour tissues. MSNs are also explored for overcoming multidrug resistance (MDR) in cancer cells.

4. Imaging and Diagnostics (Theranostic)

MSNs can be doped or conjugated with imaging agents such as quantum dots, fluorescent dyes, MRI contrast agents (e.g., Gd^{3+}, Fe_3O_4), or radionuclides. This enables their use in multimodal imaging techniques like MRI, CT, PET, and optical imaging. When combined with therapeutic agents, MSNs function as theranostic platforms, offering simultaneous diagnosis and treatment.

5. Photothermal and Photodynamic Therapy

By incorporating photosensitizers or plasmonic materials (e.g., gold nano shells), MSNs can be used in photothermal therapy (PTT) and photodynamic therapy (PDT). Upon light activation, these agents generate heat or reactive oxygen species to destroy cancer cells, often in combination with chemotherapy for enhanced efficacy.

6. Antimicrobial and Antibiofilm Applications

MSNs loaded with antibiotics or antimicrobial metals (e.g., silver, copper) exhibit strong antimicrobial activity. They can disrupt bacterial biofilms and improve drug penetration.

Functionalization with enzymes or targeting molecules enhances their specificity and effectiveness against drug-resistant bacterial strains.

7. Bone Regeneration and Tissue Engineering

Bioactive MSNs can promote bone growth and regeneration. When doped with ions like calcium or strontium, they support osteogenesis and angiogenesis. MSNs are also incorporated into scaffolds or hydrogels for applications in cartilage repair, wound healing, and dental regeneration.

8. Vaccine and Adjuvant Delivery

MSNs can deliver antigens and adjuvants in a controlled manner, enhancing immune responses. Their nanoscale size promotes uptake by antigen-presenting cells (APCs), making them attractive candidates for vaccine development, especially for subunit and mRNA-based vaccines.

9. Neurological Applications

MSNs are being explored for drug delivery across the blood-brain barrier (BBB). Functionalized MSNs can carry neuroprotective drugs, anti-inflammatory agents, or siRNAs to treat neurological disorders such as Alzheimer's disease, Parkinson's disease, or brain tumours.

10. Cardiovascular and Pulmonary Applications

MSNs are being studied for targeted delivery of anti-inflammatory and anti-thrombotic drugs to treat cardiovascular diseases. In pulmonary applications, inhalable MSN formulations can deliver drugs for asthma, cystic fibrosis, or lung cancer directly to the lungs.

Toxicity and Biocompatibility

The clinical translation of mesoporous silica nanoparticles (MSNs) as drug delivery systems, imaging agents, and theranostic tools relies heavily on their biocompatibility and toxicity profile. While MSNs have shown great promise due to their structural and functional versatility, understanding their interactions with biological systems is essential to ensure safety and efficacy [16-19].

1. Factors Influencing Toxicity

Several physicochemical properties of MSNs influence their toxicity:

- Particle Size**:** Smaller particles (<50 nm) may enter cells more readily and accumulate in sensitive organs, potentially leading to cytotoxicity. Larger particles tend to be cleared more slowly.
- Surface Chemistry and Charge: Positively charged MSNs often show higher cellular uptake but may disrupt cell membranes and increase cytotoxicity. Surface modification with polyethylene glycol (PEG) or zwitterionic coatings can reduce toxicity.
- Pore Size and Morphology**:** Variations in pore size, shape, and shell thickness can affect protein adsorption, cellular interaction, and degradation rate.

- Dosage and Exposure Time**:** High concentrations or prolonged exposure may lead to oxidative stress, inflammation, or apoptosis in cells. Toxicity is dose-dependent.

2. In Vitro Toxicity

- Cytotoxicity Assays**:** MSNs have shown variable toxicity in vitro, depending on concentration and cell type. Common assays like MTT, LDH, and live/dead staining are used to assess viability.
- Cellular Uptake**:** MSNs enter cells mainly via endocytosis. Unmodified MSNs may accumulate in endosomes or lysosomes, potentially causing local stress.
- Oxidative Stress and Inflammation: Reactive oxygen species (ROS) generation and activation of pro-inflammatory cytokines have been reported at high MSN doses.

3. In Vivo Biocompatibility and Biodistribution

- Circulation and Clearance**:** MSNs are typically cleared through the mononuclear phagocyte system (MPS), especially by the liver and spleen. Functionalization with PEG can prolong circulation and reduce uptake by macrophages.
- Degradation and Elimination**:** MSNs degrade into silicic acid ($Si(OH)_4$), which is excreted via the kidneys. The degradation rate depends on surface modification and environmental pH.
- Organ Toxicity**:** In vivo studies in mice and rats generally report good tolerability at therapeutic doses. However, very high doses may cause liver inflammation, lung fibrosis, or kidney stress.

4. Strategies to Improve Biocompatibility

- Surface Modification**:** Coating MSNs with biocompatible polymers (e.g., PEG, dextran, chitosan) or biomolecules (e.g., albumin, cell membranes) reduces immune recognition and toxicity.
- Size Optimization**:** Designing MSNs in the 50–150 nm range balances cellular uptake and systemic clearance, minimizing organ accumulation.
- Biodegradable Designs**:** Introducing stimuli-responsive linkages or hybrid compositions (e.g., organosilica frameworks) enhances degradation under physiological conditions.

5. Regulatory Considerations and Challenges

- There is no standard regulatory framework for silica nanoparticles yet, but ongoing studies are guiding safety assessment and clinical trial protocols.
- Long-term studies on chronic exposure**,** reproductive toxicity, andgenotoxicity are still limited and necessary for regulatory approval [20,21].

Conclusion:

The future of targeted drug delivery using mesoporous silica nanoparticles (MSNs) is highly promising due to their tunable structure, high loading capacity, and surface modifiability. As research advances, MSNs are expected to play a pivotal role in personalized medicine,

enabling patient-specific therapies based on molecular profiles. Integration of multiple functionalities, such as drug delivery, imaging, and real-time monitoring, will transform MSNs into powerful theranostic platforms. Next-generation MSNs will feature smart, stimuli-responsive designs that respond to pH, redox, temperature, or enzymatic cues for precise release at the disease site. Improvements in biocompatibility and biodegradability, including the development of organosilica and hybrid systems, will enhance their safety and clearance from the body. Enhanced targeting using dual-ligand systems or biomimetic coatings (e.g., cell membranes) will improve selectivity and reduce off-target effects. Artificial intelligence and machine learning may assist in optimizing MSN formulations for specific diseases and individual patients. Beyond cancer, MSNs are expected to be applied in treating neurological, cardiovascular, and infectious diseases. Efforts to meet regulatory and manufacturing standards will accelerate clinical translation. Overall, MSNs are poised to become a central tool in the next generation of targeted, efficient, and safe nanomedicine.

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AN OVERVIEW OF BISMUTH FERRITE NANOPARTICLES, USES AND PREPARATION METHODS

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Abstract:

In a single phase, multiferroic materials integrate their electrical and magnetic features. In the process of developing new technologies, these materials are preferred because of the connection between two phases. The present article describes the review on preparation of bismuth ferrite nanomaterials, nanoparticles using various techniques like hydrothermal, Pechini method and spin coating methods. The various uses of these materials are also covered in this article.

Keywords: $BiFeO_3$, Nanomaterials, Nanoparticles, Synthesis Routes, Applications

Introduction:

Several types of ordering, including ferromagnetic and ferroelectricity, are present in a single phase in multiferroic materials [1]. The characteristics of $BiFeO_3$ include its high ferroelectric Curie temperature (1103K) and antiferromagnetic Neel temperature (643K) [2].

Applications:

Multiferroic $BiFeO_3$ has several important uses in many different domains like memory devices, sensors [3], spintronics, photovoltaics, optical filters [4], multistate storage [5], micro-electronic devices [6], ultrasonic technologies [7], photocatalytic applications [8], microwave communication, satellite communications [9].

Synthesis techniques:

The number of synthesis routes has been used for the preparation of $BiFeO_3$ multiferroic such as hydrothermal method, Pechini method and spin coating technique.

Hydrothermal method:

An approach that is frequently employed to produce nanomaterials is hydrothermal synthesis [10].

The hydrothermal method for making $BiFeO_3$ nanoflakes has been reported by Wang *et al.* [11].

Cebela *et al.* [12] reported the preparation of bismuth ferrite $BiFeO_3$ particles using hydrothermal route.

Hojamberdiev *et al.* [13] reported the preparation of $BiFeO_3$ nanosized powder samples through hydrothermal technique.

Durai *et al.* [14] reported the synthesis of pure $BiFeO_3$ nanoparticles using hydrothermal appraoch and sol-gel method.

Han *et al.* [15] reported the synthesis of $BiFeO_3$ powders using hydrothermal technique.

Marzouki *et al.* [16] reported the preparation of nanopowders of $BiFeO_3$ through hydrothermal route.

Seyed Ebrahim Mousavi Ghahfarokhi *et al.* [17] reported the preparation of bismuth ferrite samples via hydrothermal process.

Cagri Ozdilek *et al.* [18] reported the formulation of undoped $BiFeO_3$ and Yb substituted $BiFeO_3$ samples using hydrothermal process.

Pechini Method:

Because of its versatility in producing perovskite membranes, layering dielectric films for capacitor manufacturing, and making multicomponent oxide materials, the Sol-Gel Pechini process gained to attention [19].

Md. Masud Parvez reported the preparation of Yttrium doped bismuth feraites nanoparticles via Pechini Sol-Gel approach [20].

According to D. S. García-Zaleta *et al.* [21], the Pechini technique was used for developing La-doped $BiFeO_3$ solid solutions.

Omid Amiri *et al.* [22] reported the formulation of $BiFeO_3$ nanoparticles through Pechini technique.

Mukherjee *et al.* [23] reported the formulation of nanoparticles of yttrium incorporated bismuth ferrite ($BiFeO_3$) using Pechini method.

Elidia A. Vetter Ferri *et al.* [24] reported the formulation of $BiFeO_3$ multiferroic samples using Pechini technique.

Sharma *et al.* [25] reported the preparation of Nd doped $BiFeO_3$ nanoparticles through Pechini modified sol-gel technique after that auto combustion route.

Md. Masud Parvez *et al.* [26] reported the formulation of bismuth ferrite ($BiFeO_3$) nanoparticles via Pechini Sol-Gel route.

Spin Coating Method:

The spin coating method is used to formulate the organic and inorganic coatings [27].

Sharmila *et al.* [28] reported the formulation of $BiFeO_3$ samples through spin coating technique.

Yasuhiro Shirahata *et al.* [29] reported the thin films of $BiFeO_3$ samples using spin coating route.

Bogle *et al.* [30] described the preparation of $BiFeO_3$ thin films using Sol gel assisted spin coating.

Kennedy *et al.* [31] reported the formulation $BiFeO_3$ thin films using a spin coating technique.

Conclusion:

The present manuscript describes the various applications of $BiFeO_3$ samples along with the reviews on different preparative techniques for the formulation of bismuth ferrite samples.

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FORMULATION TECHNIQUES OF BISMUTH FERRITE $BiFeO_3$ NANOPARTICLES AND ITS APPLICATIONS: A REVIEW

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Abstract:

A single phase of electrical and magnetic characteristics is incorporated in a multiferroic materials. The current paper gives the review on different formulation routes of bismuth ferrite nanoparticles like combustion synthesis, solid state reaction and sol gel method. This article also describes the different applications of this class of materials.

Keywords: $BiFeO_3$, Nanoparticles, Synthesis Routes, Applications

1. Introduction:

Under specific temperature conditions, multiferroic materials simultaneously manifests ferroelectric, ferromagnetic and ferroelastic characteristics [1]. The magnetoelectric effect (ME), a unique phenomenon where polarization may be controlled by an external electric field or vice versa, arises by the interaction of electric and magnetic ordered characteristics [2]. Ferroelectric Curie temperature T_C = 810ºC and antiferromagnetic Neel temperature T_N = 370ºC are the phase transition temperatures of $BiFeO_3$ [3]. With an R3c space group, $BiFeO_3$ has a rhombohedral distorted perovskite structure [4].

2. Applications:

The $BiFeO_3$ multiferroic ceramics have various applications in different fields such as, photocatalytic field [5], magnetic field sensors [6], low-power consumption [7], information storage, ultrasonic technologies [8], spintronics [9], transducers [10], multistate storage [11], microwave and satellite communications [12], supercapacitor, solar cell, battery [13], Li-ion batteries [14], high density micro-actuators [15].

3. Preparation Methods:

The present review article focuses on the preparative methods of bismuth ferrite $BiFeO_3$ nanoparticles such as:

3.1. Combustion Synthesis:

The pure $BiFeO_3$ as well as doped, codoped $BiFeO_3$ nanoparticles have been prepared using combustion synthesis route.

Bhalodia *et al.* [16] reported the formulation of $BiFeO_3$ nanoparticles by auto-combustion method.

V. Sesha Sai Kumar *et al.* [17] reported the preparation of nanocrystalline $BiFeO_3$ samples using solution combustion method.

Dovydas Karoblis *et al.* [18] reported the formulation of La and Mn codoped $BiFeO_3$ samples through sol-gel synthetic technique.

Biasotto *et al.* [19] described the microwave assisted hydrothermal process for making $BiFeO_3$ ceramic nanoparticles.

Chaudhari *et al.* [20] reported the formulation of pure $BiFeO_3$ as well as Zn substituted $BiFeO_3$ samples through self-propagating high temperature synthesis (SHS) technique.

The formation of bismuth ferrite samples using a solution combustion process was described by Penalva *et al.* [21].

Bellakki *et al.* [22] reported the formulation of undoped $BiFeO_3$ as well as Y doped $BiFeO_3$ ceramics through a solution combustion method.

Paraschiv *et al.* [23] reported the formulation of nanosized bismuth ferrite through a combustion technique.

Layek *et al.* [24] reported the synthesis of Cr doped $BiFeO_3$ nanoparticles via combustion route.

3.2. Solid State Reaction Method:

The pure, doped as well as codoped $BiFeO_3$ nanoparticles have been prepared using a solid state reaction technique.

Xi *et al.* [25] reported the formulation of $Bi_{1-x}Ba_xFe_{1-y}Co_yO_3$ samples through a modified solid state reaction technique.

Zhang *et al.* [26] reported the synthesis of Sm incorporated bismuth ferrite samples through a modified solid state reaction technique.

Gautam *et al.* [27] reported the formulation of Zr incoported $BiFeO_3$ samples using a solid state reaction technique and sol gel technique.

Muneeswaran *et al.* [28] reported the formulation of bismuth ferrite ($BiFeO_3$) ceramics using solid state reaction technique.

Londono *et al.* [29] reported the formulation of Sm doped $BiFeO_3$ samples using solid state reaction technique.

$BiFeO_3$, $Bi_{0.9}Ba_{0.1}Fe_{0.9}M_{0.1}O_3$ and $Bi_{0.80}RE_{0.2}FeO_3$ (RE=Nd, Gd, Dy) powder samples have been produced with a solid state reaction approach according to Kumar *et al.* [30].

Liu *et al.* [31] reported the formulation of $BiFeO_3$ as well as Eu substituted $BiFeO_3$ samples via solid phase reaction technique.

Yao *et al.* [32] reported the formulation of $BiFeO_3$ samples using modified solid-state-reaction technique.

Chaudhari [33] reported the formulation of Ba and Co codoped $BiFeO_3$ ceramics powders through solution combustion technique.

Naoyuki Itoh *et al.* [34] reported the formulation of $BiFeO_3$ ceramic samples through solid state reaction technique.

Shariq *et al.* [35] reported the formulation of $(BiFeO_3)_{1-x}(BaTiO_3)_x$ solid solution using solid state sintering method.

3.3. Sol- Gel Method

The pure, doped as well as codoped $BiFeO_3$ nanoparticles have been prepared using sol-gel method.

Mao *et al.* [36] reported the formulation of pure $BiFeO_3$, Dy doped $BiFeO_3$ and Dy, Cr codoped $BiFeO_3$ samples through carbon microsphere assisted sol–gel technique.

Taryana *et al.* [37] reported the formulation of nanoparticles of $BiFeO_3$ samples using sol gel technique.

Mubarak *et al.* [38] reported the formulation of $BiFeO_3$ nanoparticles using sol-gel technique.

Sherkar *et al.* [39] reported the formulation of $BiFeO_3$ nanoparticles via sol-gel auto-combustion method.

Sol-gel synthesis of Eu-doped $BiFeO_3$ samples has been reported by Thang *et al.* [40].

Lin *et al.* [41] reported the formulation of Ca incorporated $BiFeO_3$ nanoparticles through sol gel route.

M N Abdillah *et al.* [42] reported the formulation of $BiFeO_3$ samples via sol-gel technique.

Vanga *et al.* [43] reported the formulation nanoparticles of Nd, Cr codoped $BiFeO_3$ samples using sol-gel route.

Sinha *et al.* [44] reported the formulation of $BiFeO_3$ nanoparticles using sol gel technique.

Arora *et al.* [45] reported the nanoparticle formulation of Ce doped $BiFeO_3$ materials through sol gel technique.

Conclusions:

This review article discusses the various synthesis methods of pure, doped and codoped $BiFeO_3$ nanoparticles and its applications in number of fields.

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FROM MARGINS TO MAINSTREAM: TRACING WOMEN'S JOURNEY IN SCIENCE AND TECHNOLOGY IN INDIA

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Abstract:

The involvement of women in science and technology in India differs significantly from where it was to where it is today. As a society, we have travelled from the periphery of participation to increased contributions by women. In this chapter we provide a review of where we started, how we got here, the relevant policies, institutional supports, and social movements. We will look at how socio-cultural factors, through educational reform, changed over time to impact women's participation in science, technology, engineering and mathematics (STEM) fields, as well as policy-initiated schemes such as Women Scientists Scheme and Gender Advancement for Transforming Institutions (GATI). This book chapter discusses various case studies of women scientists, innovators, and technologists in a range of disciplines, such as space research, biotechnology, information technology, and engineering. While these case studies detail the challenges faced by women, they also show how obstacles were overcome to enhance their contributions to their these disciplines. Finally, we discuss current challenges to women's participation including gender bias, glass ceiling, and lack of mentorship, as well as practical approaches for institutional interventions compassionate to women's equity in science and technology. Altogether, this chapter contributes to the literature and empirical voices surrounding gender equity in STEM fields and will have broader implications for all stakeholders (not only in the education and academic sector) who aim to support women in science and technology in India.

Keywords: STEM, Space Research, Gender Equity, Educational Reform and Social Movements

1. Introduction:

Women's engagement in science and technology in India has been uneven but increasingly progressive. In the past, women's work in these fields was not recognized or valued because of societal norms that limited women's access to education or careers in these fields. There are some remarkable women who overcame barriers to education in science, such as Anandibai Joshi, the first female doctor in India, and Janaki Ammal, a botanist. These women worked as agents of change for women in science. With independence in 1947, India implemented new educational policies and scientific policies to democratize access to education,

and policies promoting a scientific temper in the country. Initially, these educational or scientific policies reflected gender, but women's inclusion in science was limited.

The 21st century has seen reconceptualization of gender equality through specific programmes and schemes (for example, the Department of Science and Technology's Women Scientists Scheme, the GATI programme, etc.) building towards developing a more inclusive ecosystem for research. The chapter seeks to map the historical developments in India regarding women in STEM while capturing the relationship of policy, societal direction, and individual agency. It incorporates both historical and contemporary developments of women's participation in STEM, considering systemic enablers and obstacles to participation. With case studies, the chapter goes further by recognizing that the reality of women's participation in STEM is more than data, and representation and role models are important. In essence, we aspire to determine good practice and best fit, to initiate interpretations that strengthen women's role in supporting India's science and technology future.

2. Historical Context

Women entering science and technology in India have their origins in the colonial period, with strict gender norms and limited access to education for women. However, there were some trailblazers. Anandibai Joshi became the first female physician in India in the 1880s and Janaki Ammal was a notable botanist and cytogeneticist in the mid-twentieth century. Missionary schools and social reform movements, led by British intellectuals, such as Raja Ram Mohan Roy and Ishwar Chandra Vidyasagar advocated for women's education during British rule and were, arguably, the only sources of educational access available then. However, science had male access. The first time women began to gain access to higher education in the sciences occurred in the twentieth century. Finally, with the establishment of the Indian Institute of Science (IISc) in 1909 and universities granting science degrees between 1900 and 1930, women have entered science with some success.

Following independence, India's constitution provided equal rights for everyone including a right to education and employment. This legal scaffolding was essential but prejudice existed. However, under the Nehruvian vision of scientific temper and national development, there was a significant emphasis on science and technology, which indirectly encouraged women's participation. In the 1970s and 1980s, science courses increasingly saw women's participation primarily due to the growth of public education and urbanization. Furthermore, professional groups like the Indian Women Scientists' Association, founded in 1973, provided a forum for women to network and advocate.

Although Indian women's representation in STEM remained low, their increasing presence in universities and research institutes was a crucial foundation for the policy-driven efforts of the 21st century. Although barriers of gender stereotyping, role models, and family

obligations persisted, there was a strong inheritance of the early trailblazers and changing sociocultural norms that began to make gender inclusivity an expectation instead of the exception. This context primed women's potential in STEM which was next for institutional and governmental support to assist in mainstreaming women within science and technology through gender inclusivity efforts.

3. Policy Impact and Institutional Support

In the last twenty years, the Government of India has taken various policy actions to improve gender equity in science and technology. A great example is the Women Scientists Scheme, launched by the Department of Science and Technology (DST) in 2002. The WOS provides fellowships to women who have taken a career break to care for family commitments, to return to scientific research. Another landmark initiative is 'Gender Advancement for Transforming Institutions' which is an Indo-UK collaboration as part of the Newton Bhabha Fund. GATI seeks to effect gender equality in institutions and support structural change to achieve it in higher education and research organisations. These organisations commit to a process of self-reflection and ultimately, gender audits and equity action plans, on a voluntary basis.

Apart from this there are also the Knowledge Involvement in Research Advancement through Nurturing (KIRAN) scheme which is a suite of schemes to support women scientists / across all discipline. There are also some sector-specific efforts such as fellowships by the Indian Council of Medical Research (ICMR), Indian Space Research Organisation (ISRO) and Department of Biotechnology (DBT) to promote transitions in women's participation. Establishing institutional supports for women researchers through the creation of women-focused research chairs, established women's universities, and funding for women-led start-ups by the Biotechnology Industry Research Assistant Council (BIRAC) provides places to receive and distribute support that, beyond funding, provides mentorship and incubation support.

Organizations also have varying degrees of awareness and support for women of the schemes by establishing women's cells and committees, however the overarching review and monitoring mechanisms are weak, and participation in exotic projects, where voluntary programs such as GATI are concerned, differs between institutions. While these actions are encouraging, they concrete changes primarily signal a shift from passive to active women's role change-based intervention.

Mentorship, flexible workspaces, re-entry fellowships all signal an understanding of the systemic barriers to advancement for women in STEM. When implemented, these programs can transform the existing legacy of women being marginalized into a more equitable, representative space for Indian science and technology. Ultimately, whether or not these programs will be

transformative is not only dependent on sustained funding, support and accountability for institutions and institutions but also advocacy.

4. Barriers to Participation

Women in science and technology in India face multiple-layered challenges that impede their ability to participate fully. While there is a reform agenda underway, and awareness of gender inequality is growing, women's presence in the science and technology fields remains in question. One of the continuing issues is the persistent gender stereotype that positions science and technology as male domains. Upon childhood, or even before, girls are socialized toward accepting gender norms about appropriate roles. For instance, families employ social and cultural norms in relation to domestic and caring responsibilities as a way to reinforce expectations of women above pursuing education in STEM.

The challenge of a woman's family responsibilities in addition to struggling to find supportive systems is exacerbated by this challenge. In contrast, women's responsibilities as wives, mothers and daughters somewhat obliges them to demonstrate care at home, obligations that outperform their attitudes toward ambition and their opportunities in the workplace. For example, child cares and other maternity-friendly practices or possibilities for flexible work practices, one-day return to work after maternity leave, or simply the comfort of women's informal or formal partnerships, impact retention among women scientists. Both implicit and explicit bias and gender discrimination persist. It is alleged that women in science experience a gendered hiring and promotion process in consideration of their credentials and competency in STEM. They feel their gender limits their access to legitimate leadership roles and available resources, along with role models or mentors to engage in the mission to fill what is referred to in academia as the 'leaky pipeline'.

Consequentially, women exit STEM in a systematic or gradual progression for a variety of reasons, one of which is related to their unique experience in academia, and the dynamics of never having genuine peers (women) to form professional connections. Upon the realization of institutional culture, it becomes clear that institutions introduce an exclusionary atmosphere that a woman must work in for their whole career within networks which are led discussed in totally male networks of fathers, sons, collegiates, and/or responsibly engaged as family. In addition, harassment and weak grievance mechanisms are limiting many people’s willingness to stay in research and development. There is also an inequity issue, especially concerning funding and publication opportunities, which unfortunately means the woman scientist still gets less credit (and fewer promotion options) for her work. Several studies have shown that women scientists, on average, receive smaller research grants than their male counterparts, and a smaller proportion of women scientists serve on high-profile scientific committees and award panels. As such, it is

often emphasized that when we talk about women's equity, we must also consider intersectionality.

Women scientists who are from rural areas, or lower socio-economic groups or marginalized communities may find themselves at the compounded disadvantage of not being able to access quality education or quality research opportunities. All these barriers suggest that to address them will require systematic changes: systematic changes that include changes to institutions and practices, policy changes that address women's concerns and needs, change education to include sensitivity training to all age groups, and monitoring changes as part of next stage approaches. When all women have equal access to the scientific ecosystem, not only does equity improve, but also enhance innovation by leveraging the full potential of the talent pool.

5. Contemporary Success Stories

To illustrate the growing role of Indian women in science and technology, the following table presents more than twenty contemporary success stories. Each entry highlights key individuals, their contributions, the field they operate in, and the impact of their work.

5.1 Trends Observed

i. **Multidisciplinary:** Many Indian women have excel across varied domains i.e. from molecular biology to astrophysics
ii. **Global Impact:** Various Indian women are changing the face of world science with institutes like WHO, NASA, and CERN.
iii. **Institutional Roles:** Some have headed or established major research institutions and carved a path for future women leaders.
iv. **Barrier Breaking:** Nearly all have engaged with systemic gender biases and most (if not all) are firsts in their field.

The mix of policies, mentorship and access to education continues to play a strong role in shaping these narratives; though social biases remain relevant, and lack of user-representative membership remains a pertinent cause for concern. Facilitating the path for more women into STEM, and retaining them in STEM must address structural inequities and supportive institutional pathways. These founders and pioneers function as human navigators to a viable model for scientific development and inclusion in India.

S. No.	Name	Field of work	Contribution	Impact
1.	Tessy Thomas	Aerospace / Defence	Led Agni-IV and Agni-V missile projects at Defence Research and Development Organization (DRDO).	First woman to head a missile project in India and role model for women in defence science
2.	Kalpana Chawala	Aerospace Engineering/ Space Exploration	First Indian women in space and conducted scientific experiments	Inspired global interest in space science and empowered women in space science.
3.	Gagandeep Kang	Medical Science / Virology	Developed rotavirus vaccine and researched enteric diseases	First Indian woman elected to Royal Society, and major influence on child health and vaccine development.
4.	Ritu Karidhal	Space Science	Deputy Operations Director for Mangalyaan and led Chandrayaan mission.	Symbol of female leadership in ISRO and space exploration.
5.	Soumya Swaminathan	Public Health / Medicine	WHO Chief Scientist; tuberculosis and HIV research	Guided WHO's COVID-19 response and shaped global health policies
6.	Priya Abraham	Virology / Public Health	Directed National Institute of Virology during COVID-19	Strengthened India's diagnostic infrastructure and vaccine testing protocols.
7.	Shubha Tole	Neuroscience	Pioneered work in brain development and evolution	Recipient of Infosys Prize and increased understanding of neurodevelopment
8.	Rohini Godbole	Particle Physics	Research on Higgs boson and supersymmetry	Leading contributor to India's participation in Conseil Européen pour la Recherche Nucléaire which translates to European Council for Nuclear Research in English (CERN)

9.	Nandini Harinaath	Space Technology	Worked on 14+ missions including Mangalyaan	One of the main inspirations behind Mission Mangal and promoted visibility of women in ISRO
10.	Kiran Mazumdar-Shaw	Biotechnology / Entrepreneurship	Founded Biocon and led affordable drug production	Made insulin and other critical drugs affordable and global biotech leader.
11.	Indira Nooyi	Business and Corporate Leadership	Led PepsiCo as CEO and promoting healthier products and global business growth	Pioneered women leadership in business and inspiring global corporate diversity and sustainability initiatives.
12.	Vandana Sharma	Nuclear Engineering	Ensured operational safety at Nuclear Power Corporation of India Limited (NPCIL)	Enhanced India's nuclear safety standards.
13.	Manju Sharma	Biotechnology / Policy	Headed Dept. of Biotechnology; started several research schemes	Enabled institutional support for women scientists.
14.	Archana Sharma	Particle Physics	Worked on the Large Hadron Collider at CERN.	Represented India in global high-energy physics and encouraged diplomacy in science.
15.	Sunita Narain	Environmental Science / Policy	Led Centre for Science and Environment and member of climate change councils.	Influenced India's climate and environmental policy.
16.	Madhuri Kanitkar	Medicine / Armed Forces Leadership	Paediatrician and high-ranking military official	First woman dean at Armed Forces Medical College (AFMC), and a trailblazer in medicine and military leadership.
	Sunita Williams (Indian Descent)	Space exploration, aeronautical engineering, and naval aviation operations.	Commanded International Space Station (ISS) expeditions, performed seven spacewalks and advanced space science.	Inspired global youth, promoted women in STEM and space research.

17.	Aditi Pant	Oceanography	First Indian woman to visit Antarctica and studied polar ecosystems	Paved the way for Indian women in polar research.
18.	Yamuna Krishnan	Chemical Biology	Developed Deoxyribonucleic Acid (DNA) nanodevices to monitor cell behaviour	Leading researcher in DNA-based technology and global recognition.
19.	Leena Gade	Motorsports Engineering	First female race engineer to win Le Mans.	Broke gender barriers in motorsports and mechanical engineering.
20.	Swati Mohan	Aerospace / NASA	Guided Mars 2020 rover landing operations.	Became a symbol of Indian-origin success in international space missions.
21.	Seema	Biomedical Sciences	Research on cytoskeletal proteins and cancer.	Advanced understanding of cancer metastasis; significant role in U.S. biomedical research.
22.	Rajeswari Chatterjee	Microwave Engineering (Historical)	Early work on radar and microwave technology at IISc	First woman engineering faculty at IISc and foundational work in Indian defence technology.

6. Future Directions and Recommendations

As India aims to advance to become a global leader in science and technology, it is essential to ensure that women are fully and equitably engaged in these sectors. Ultimately, the future of women in STEM is fundamentally dependent on our ability to take proactive text-style, lasting action on multiple fronts.

6.1 Building Educational Foundations: Engagement with STEM starts early, therefore, we need gender-inclusive and preferably transformative, curricular and pedagogical practices, that disrupt stereotypes. Interventions such as science clubs, coding boot camps, and innovation labs in schools can inspire STEM trajectories for young women - especially in rural areas and historically marginalized communities.

6.2 Developing Mentorship and Networks: Appropriate mentorship programs are particularly important in growing and retaining female talent. Linking young female researchers with experienced scientists will provide valuable guidance and opportunities for career development. Having national expertise databases for women can also increase visibility and representation on panels, committees, and in the media.

6.3 Supporting Work-Life Balance: Flexible working environments (e.g. hybrid work, part-time work), and career-track parental leave options should incentivize women's career aspirations at various life stages and in various situations. Structuring institutions to support child care and acknowledging the importance of shared domestic responsibilities will be pivotal to sustaining women's participation.

6.4 Expanding Policy Outreach: Initiatives such as Women in Science (WOS) and Gender Advancement through Transformative Innovation (GATI) need to be scaled and embedded in all research institutions. Regular audits and public dashboards, for example, will enhance transparency and accountability. When institutions formalize incentives for achieving gender equity metrics, they can expect sustained commitment.

6.5 Supporting Women Entrepreneurs in Technology: Templates from programmes such as BIRAC's support for women start-ups, should be replicated. The process of accessing seed funding, business mentoring, and patents must be streamlined for women against systems, among them social conventions entrenched against women in technology to flourish as funders.

6.6 Incorporating intersectionality: Any future strategy should acknowledge that caste, class, geography, and disability are aspects of differentiated inclusion. Targeted schemes for disadvantaged communities and technology training to enhance digital literacy can assist.

6.7 Creating a culture of respect and safety: Gender sensitisation workshops complemented with a zero-tolerance stance to all forms of harassment, and formal grievance redressal mechanisms will have significant impact. Creating space for inclusive leadership within institutions will break down institutional cultures.

Conclusion:

The past one hundred years represents the resilience, innovation, and fundamental alteration of women's engagement in science and technology in India. From early trailblazing individuals who developed early scientific engagement for women in India to systemic policy interventions in the 21st century that considered women's engagement in recruits to science and technology fields, represented the hard work and excitement of progress. This sentinel chapter explored various forms of women's participation and advancement in STEM, from historical exclusions to the emerging leadership of women, through empirical analysis and case studies which demonstrated the complex diversity, plurality, and dynamics of women's contributions to science and technology. Despite progress through engagement, advancement and participation is not uniformly experienced. Stereotypical gender roles, work-life balance, implicit bias, institutional inertia, all exert constraints on the participation and advancement of women in science, technology, engineering and mathematics. Nevertheless, the ever-growing ecosystem of support policies such as Women in Science and Gender Advancement in Science, and Technology, changes to education, and profiles of role models, among others are establishing trajectories for a healthy future.

The case studies show that women in India are engaging and succeeding in areas as diverse as space research, virology, quantum physics, and environmental science. These case studies are inspirational stories for younger generations and proof that systemic change is possible when there is intent, resource investment, and implementation. Now comes the commitment, where the journey ahead needs to be about inclusion rather than representation, about leadership rather than getting opportunities. At this pivotal moment, the equitable access, affirmative mentoring, and intersectional policy planning will be used to not only sustain the strides made, but to expand them. The rise of women in science and technology is not just a gender issue, it is a national imperative. India's goals for innovation and global competitiveness will only be realized through the full harnessing of its human capital, of which women scientists, technologists, and innovators are a critical part. If we act boldly, and systemically, the future can be equitable, excellent, and innovative.

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INTEGRATING VERTICAL FARMING AND CONTROLLED ENVIRONMENT AGRICULTURE FOR FUTURE FOOD SECURITY

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Introduction:

Vertical Farming (VF) and Controlled Environment Agriculture (CEA) have emerged as pioneering approaches to address the mounting challenges of modern agriculture. VF involves cultivating crops in vertically stacked layers, typically within repurposed urban infrastructure, thereby optimizing spatial efficiency and enabling hyper-local food production. CEA, on the other hand, employs sophisticated technologies to regulate environmental variables such as light intensity, temperature, humidity, CO_2 concentration, and nutrient delivery with high precision. When integrated, these systems synergistically enhance crop productivity, resource efficiency, and resilience to climate variability. Their convergence signifies a paradigm shift towards data-driven, environmentally sustainable, and space-conscious food systems that can play a critical role in ensuring future food security.

The world is facing an unprecedented food security crisis driven by rapid population growth, climate change, land degradation, and increasing resource scarcity. According to the UN, food production must increase by at least 60% by 2050 to meet the nutritional needs of a projected 9.7 billion people. Traditional agriculture, constrained by finite arable land and water resources, is struggling to keep pace with demand. This subsection explores the scope, causes, and implications of global food insecurity and sets the stage for innovative solutions.

Urbanization is reshaping the global demographic and spatial landscape, with more than half the world's population now living in cities. This urban expansion exerts pressure on peri-urban agricultural zones and reduces the land available for food production. It also increases the distance between production and consumption, contributing to food waste and carbon emissions. This section examines the challenges posed by urban growth and its adverse effects on traditional agriculture.

To bridge the gap between growing demand and limited resources, agricultural innovation has become essential. Precision agriculture, biotechnology, robotics, and data-driven systems are transforming farming practices. Among the most promising innovations are Vertical Farming (VF) and Controlled Environment Agriculture (CEA), which enable food production in non-traditional settings with high efficiency and minimal environmental impact. This section

highlights the rise of tech-enabled agriculture and its potential to address pressing food system challenges.

Overview of Vertical Farming and Controlled Environment Agriculture

Vertical Farming (VF) and Controlled Environment Agriculture (CEA) are complementary innovations reshaping the way food is grown and distributed. VF is characterized by the vertical stacking of plant production units within urban or semi-urban structures, optimizing space and minimizing land usage. It typically employs hydroponic, aeroponic, or aquaponic systems to nurture crops in controlled environments without soil. CEA, on the other hand, is a broader framework that utilizes technological systems to manipulate and maintain optimal growing conditions, such as temperature, humidity, light, and CO_2 levels, regardless of external climate variability.

Both VF and CEA operate on the principles of precision agriculture, environmental sustainability, and resource optimization. VF enables hyper-local production, reducing transportation emissions and enhancing freshness, while CEA maximizes crop yields through real-time monitoring and automation. Their independent functionalities already offer significant benefits; however, when integrated, they form a highly resilient, high-efficiency model of food production. This synergy lays the foundation for a transformative shift in agricultural practices, particularly relevant in urban contexts and climate-sensitive regions.

Vertical Farming

Vertical Farming (VF) refers to an innovative agricultural method where crops are cultivated in vertically stacked layers, often within controlled indoor environments such as high-rise buildings, modular shipping containers, or repurposed industrial spaces. This spatially efficient approach is designed to address the limitations of traditional agriculture in land-scarce and urban regions. Vertical farms typically utilize soilless cultivation systems namely hydroponics, aeroponics, or aquaponics which facilitate nutrient delivery directly to the plant roots, significantly reducing water and land use.

VF systems are characterized by their integration with advanced technologies, including automated lighting (primarily LED), climate control systems, nutrient dosing equipment, and real-time monitoring via sensors and Internet of Things (IoT) platforms. These components enable precise control over environmental parameters such as light intensity, temperature, humidity, and CO_2 levels, fostering optimal crop growth year-round irrespective of seasonal or geographical limitations. By producing food closer to consumption centres, vertical farming not only enhances urban food security and supply chain resilience but also reduces transportation emissions and post-harvest losses.

Controlled Environment Agriculture

Controlled Environment Agriculture (CEA) refers to a technologically intensive approach to farming where key environmental factors—such as light, temperature, humidity, carbon dioxide concentration, and nutrient availability—are meticulously regulated to maximize crop productivity and quality. By eliminating reliance on external climate conditions, CEA enables consistent, year-round cultivation in virtually any location.

Core principles of CEA include precision control, automation, resource efficiency, and biosecurity. These systems are typically housed within greenhouses, growth chambers, or fully enclosed plant factories, where inputs are monitored and adjusted in real-time using integrated technologies. Key components include LED lighting systems tailored to specific plant photoperiods and spectra, HVAC systems for thermal and humidity regulation, CO_2 enrichment for photosynthetic enhancement, and computer-controlled nutrient delivery systems. Sensors and Internet of Things (IoT) platforms play a critical role in ensuring optimal growing conditions through data-driven decision-making.

Ultimately, CEA represents a paradigm shift from reactive to proactive crop management, offering a scalable solution to challenges posed by climate variability, urbanization, and the need for sustainable intensification of food production.

Historical Development and Evolution of VF and CEA

The historical roots of Vertical Farming (VF) and Controlled Environment Agriculture (CEA) can be traced back to ancient and early modern innovations such as the Hanging Gardens of Babylon and 17th-century greenhouse cultivation in Europe. However, their modern forms began to take shape in the 20th century with the advent of hydroponics and climate-controlled greenhouses. The conceptual framework for vertical farming gained global recognition in the early 2000s, largely due to the work of Dr. Dickson Despommier, a professor at Columbia University. He envisioned multi-story urban farms as a response to food insecurity, environmental degradation, and urban population growth.

Since then, both VF and CEA have undergone rapid evolution, fuelled by advancements in environmental control systems, LED lighting, data analytics, and artificial intelligence. The proliferation of smart technologies and urban architectural innovations has enabled the construction of highly efficient, modular, and scalable vertical farms. Countries like Japan, the Netherlands, Singapore, and the United States have emerged as leaders in implementing and refining these systems. Government support, private investment, and academic research have further accelerated adoption, pushing VF and CEA from experimental concepts to commercially viable and increasingly mainstream solutions for urban and climate-resilient food production.

Comparative Analysis with Traditional Agriculture

Traditional agriculture, grounded in centuries of open-field cultivation, is inherently dependent on natural cycles, soil quality, rainfall patterns, and climatic conditions. This reliance often results in seasonal variability, vulnerability to pests and diseases, and unpredictable yields—factors increasingly exacerbated by climate change. Moreover, conventional methods typically require expansive land areas and large volumes of water, leading to deforestation, soil degradation, and depletion of natural resources.

In contrast, Vertical Farming (VF) and Controlled Environment Agriculture (CEA) represent technologically advanced systems that decouple food production from these environmental uncertainties. These systems offer precision control over growth parameters, enabling consistent, high-quality yields with significantly reduced resource input. They can be implemented in urban settings, utilize less land and water, and generate fewer emissions associated with transportation and field operations.

However, the transition to VF and CEA is not without challenges. These include substantial capital investment, dependence on reliable energy sources, sophisticated operational expertise, and current limitations in crop diversity—particularly for staple grains and root vegetables. Despite these drawbacks, VF and CEA present a compelling alternative to traditional agriculture, especially in regions facing land scarcity, climate volatility, or the need for localized food systems.

Integration Potential of VF and CEA

The integration of Vertical Farming (VF) and Controlled Environment Agriculture (CEA) presents a transformative model for addressing contemporary food system challenges. VF's vertical spatial optimization complements CEA's precision control over environmental variables, allowing for unprecedented efficiency and scalability in crop production. This integrated approach not only maximizes yield per unit area but also enhances resource-use efficiency, significantly lowering water, nutrient, and land requirements.

By operating independently of external weather conditions and geographical limitations, integrated VF-CEA systems provide a consistent and predictable food supply, vital in the face of climate disruptions. Urban environments, in particular, benefit from such systems through reduced food miles, fresher produce, and improved self-reliance. These systems also offer potential for modular scalability, adaptability to underutilized urban spaces, and resilience against supply chain disruptions.

Despite requiring high initial capital and energy inputs, the integration of VF and CEA is increasingly supported by advancements in automation, AI, and renewable energy, improving their viability and sustainability. Overall, these integrated systems can serve as a cornerstone of

future food strategies, contributing substantially to food security, ecological preservation, and climate resilience in both developed and developing contexts.

Core Technologies and Systems

This section elaborates on the essential technologies underpinning vertical farming and controlled environment agriculture. These technologies form the backbone of modern smart agriculture and facilitate the integration of VF and CEA to deliver high-efficiency, climate-resilient food systems.

1. Hydroponics, Aeroponics, and Aquaponics

Hydroponics involves growing plants in a nutrient-enriched water solution, allowing precise control over nutrient delivery and eliminating the variability of soil quality. This method significantly reduces water usage by up to 90% compared to traditional agriculture and minimizes the risk of soil-borne diseases.

Aeroponics advances efficiency further by suspending plant roots in air and periodically misting them with a nutrient-rich solution. This system maximizes oxygen exposure to the roots, leading to accelerated growth rates and enhanced nutrient absorption. It is especially valuable in high-density vertical farm configurations due to its low water and substrate requirements.

Aquaponics integrates aquaculture (fish farming) with hydroponics, forming a closed-loop, symbiotic ecosystem. In this system, fish waste provides an organic nutrient source for plants, while the plants purify the water, which is then recirculated back to the fish tanks. This method not only reduces water consumption but also produces both plant and animal protein, offering a diversified food production system.

Collectively, these techniques enable high-efficiency, environmentally friendly farming with minimal resource input and high scalability, making them ideal for urban and resource-limited environments.

2. Environmental Control Systems: Light, Temperature, Humidity

Environmental control technologies form the backbone of Controlled Environment Agriculture (CEA), allowing growers to establish and maintain optimal conditions for plant development across all growth stages. Among these, LED lighting is a critical component, engineered to simulate sunlight with customizable wavelengths and intensities tailored to different crop types and developmental phases—such as germination, vegetative growth, and flowering. This flexibility enhances photosynthetic efficiency and energy use.

Temperature and humidity regulation is managed through sophisticated HVAC (Heating, Ventilation, and Air Conditioning) systems, which maintain stable microclimates essential for consistent growth, disease prevention, and metabolic optimization. These systems are often integrated with real-time sensors and climate control algorithms to dynamically adjust conditions based on plant needs and environmental fluctuations.

By decoupling crop production from natural seasonal variations and unpredictable weather, these environmental control systems enable uninterrupted, year-round cultivation with superior yield and quality outcomes. Furthermore, they enhance resource efficiency, reduce reliance on chemical inputs, and facilitate farming in unconventional or inhospitable locations such as urban rooftops, deserts, and cold climates.

3. Automation, Sensors, and Internet of Things (IoT)

Automation, sensors, and IoT technologies are fundamental enablers of smart farming within VF and CEA systems, driving operational efficiency, consistency, and scalability. Automation encompasses tasks such as nutrient dosing, irrigation, lighting, and harvesting, significantly reducing labor requirements, minimizing human error, and ensuring standardized crop management practices.

Sensors play a pivotal role by continuously monitoring key environmental and plant health parameters including pH, electrical conductivity (EC), temperature, humidity, light intensity, CO_2 levels, and moisture content. These real-time inputs allow for timely adjustments that optimize plant growth, prevent disease, and conserve resources.

The Internet of Things (IoT) acts as the connective tissue among these components, linking sensors, control systems, and data platforms. IoT-enabled systems facilitate remote monitoring, predictive maintenance, and automated responses via cloud-based dashboards and AI-driven analytics. This integration allows growers to manage multiple facilities simultaneously, implement data-driven cultivation strategies, and quickly respond to environmental fluctuations, thus enhancing productivity and sustainability.

Together, automation, sensors, and IoT create a robust, adaptive infrastructure that supports precision agriculture, improves traceability, and reduces the ecological footprint of food production systems.

4. Data-Driven Agriculture and Artificial Intelligence

Data-driven agriculture and Artificial Intelligence (AI) are revolutionizing how decisions are made within Vertical Farming (VF) and Controlled Environment Agriculture (CEA) systems. AI algorithms and machine learning models process vast datasets collected from environmental sensors, historical crop performance, and system outputs to uncover patterns, optimize growing strategies, and automate routine decisions.

One key application is predictive analytics, which enables accurate forecasting of yield, nutrient requirements, pest and disease risks, and energy consumption. This helps in planning resource allocation, reducing input waste, and maximizing return on investment. AI can also facilitate dynamic adjustments in lighting, irrigation, and climate control, adapting cultivation conditions in real time based on plant responses and external factors.

Advanced data platforms allow centralized monitoring and benchmarking across multiple production units, improving operational transparency and traceability. Furthermore, machine vision and robotics, guided by AI, are increasingly used for automated harvesting, plant health assessment, and quality grading.

By integrating AI and data analytics, VF and CEA systems become more resilient, scalable, and precise—supporting informed decision-making, reducing labor reliance, and accelerating innovation in sustainable food production.

5. Energy Sources and Sustainability Considerations

Energy consumption is one of the most critical factors influencing the environmental and economic viability of Vertical Farming (VF) and Controlled Environment Agriculture (CEA) systems. These operations are particularly energy-intensive due to their reliance on artificial lighting, HVAC systems, and automation technologies. Consequently, improving energy efficiency and integrating renewable energy sources are essential to enhancing sustainability.

To mitigate their carbon footprint, many VF and CEA operations are increasingly powered by renewable energy sources such as solar panels, wind turbines, and geothermal systems. These sources can be integrated with energy storage technologies to ensure a stable supply, even during periods of low generation. Additionally, energy-efficient innovations—such as optimized LED lighting with variable spectrums, heat recovery ventilation systems, and advanced insulation materials—are being widely adopted to reduce operational energy demands.

Sustainable system design also includes strategies like energy cascading, where waste heat from one process is repurposed to heat other parts of the facility, and closed-loop systems that reduce resource wastage. Waste management is further enhanced through composting plant residues and integrating bioenergy generation, thereby supporting circular economy models.

Moreover, smart energy management systems driven by AI and real-time monitoring tools can dynamically adjust energy consumption based on operational needs, minimizing waste and cost. When combined, these innovations contribute to creating energy-resilient and low-emission agricultural models that align with global climate and sustainability goals.

Together, these core technologies form the foundational infrastructure that empowers vertical farming and controlled environment agriculture to operate at scale, maintain high resource-use efficiency, and swiftly adapt to environmental or market changes. By leveraging innovation and precision tools, these systems are positioned to transform food production and distribution in ways that directly address pressing global food security concerns.

Vertical Farming and CEA: Complementary Strengths

1. Enhancing Crop Yield and Quality

Integrated Vertical Farming and Controlled Environment Agriculture systems provide optimal conditions that significantly enhance both the quantity and quality of crop yields. Precise

control over light spectra, temperature, humidity, CO_2 levels, and nutrient delivery ensures ideal photosynthetic activity, resulting in faster growth cycles and higher biomass accumulation. Moreover, the ability to monitor and adjust parameters in real time minimizes stress-induced physiological damage, producing visually and nutritionally superior crops. Many VF and CEA operations consistently achieve yields that are multiple times higher per square meter than traditional agriculture, all while maintaining uniformity and food safety.

2. Space Optimization in Urban Settings

One of the most striking benefits of VF and CEA is their ability to maximize food production in constrained urban spaces. By leveraging vertical stacking and compact modular designs, these systems can be implemented on rooftops, in basements, inside shipping containers, or within repurposed buildings. This spatial efficiency is critical in densely populated cities where land availability is limited. Additionally, producing food closer to consumption points reduces food miles and associated carbon emissions, supporting local economies and enhancing urban food sovereignty.

3. Water and Nutrient Efficiency

VF and CEA systems are designed for minimal input wastage, using advanced irrigation technologies such as closed-loop hydroponics, aeroponics, and aquaponics. These methods dramatically reduce water consumption—often by up to 90% compared to conventional field farming—by recycling runoff and eliminating evaporation losses. Nutrient solutions are carefully monitored and dosed based on plant needs, maximizing uptake and reducing leaching or environmental contamination. This precise management results in resource-efficient farming practices that are particularly valuable in water-scarce regions.

4. Year-Round and Climate-Resilient Production

The controlled environments in VF and CEA systems decouple crop production from seasonal and climatic dependencies. This enables continuous, year-round cultivation regardless of external weather conditions, geographic location, or natural disasters. Such predictability not only stabilizes supply chains but also ensures a steady income for producers. These systems are particularly advantageous in regions affected by extreme weather patterns, offering a reliable alternative in the face of climate volatility and agricultural disruption.

5. Minimizing Pesticide and Chemical Use

The enclosed and regulated nature of VF and CEA environments substantially reduces the risk of pest and pathogen invasion, minimizing the need for synthetic pesticides and herbicides. Many facilities rely on integrated pest management (IPM) practices, biological controls, and physical barriers such as air filters and insect screens. The result is cleaner, safer produce with fewer chemical residues, meeting increasing consumer demand for healthier,

sustainably grown food and reducing the ecological impact of conventional chemical-intensive agriculture.

Challenges and Limitations

1. High Initial Capital and Operational Costs

Despite their long-term benefits, Vertical Farming (VF) and Controlled Environment Agriculture (CEA) systems are often constrained by substantial upfront capital requirements. These costs arise from the need to invest in advanced technologies, including LED lighting systems, HVAC units, automation infrastructure, hydroponic or aeroponic systems, and real-time monitoring equipment. Operational expenses, particularly electricity consumption and system maintenance, also contribute significantly to total expenditure. For many startups and small-scale farmers, these financial barriers can hinder adoption and scalability, necessitating innovative financing models, public-private partnerships, and government subsidies to reduce the burden.

2. Energy Dependency and Carbon Footprint

VF and CEA operations are highly energy-dependent due to their reliance on artificial lighting, climate control, and continuous monitoring systems. This dependency can result in a considerable carbon footprint, especially when non-renewable energy sources are used. Although the integration of solar, wind, and geothermal energy has shown promise in reducing emissions, the cost and infrastructure required for large-scale renewable integration remain challenges. Energy optimization technologies, dynamic control systems, and more efficient LED designs are essential for minimizing energy intensity and ensuring sustainability.

3. Technological and Knowledge Barriers

Implementing VF and CEA systems demands a high level of technical expertise, which can be a barrier in regions with limited access to education or technological infrastructure. Farmers and operators must be trained in areas such as environmental control, nutrient management, software-based automation, and data analytics. Additionally, a lack of standardized best practices and fragmented knowledge-sharing platforms limits the widespread dissemination of know-how. Strengthening educational programs, vocational training, and extension services is critical to overcoming this challenge.

4. Limited Crop Diversity and Consumer Acceptance

Currently, VF and CEA systems primarily focus on fast-growing, high-value crops such as leafy greens, herbs, and microgreens. The cultivation of staple crops like wheat, rice, and root vegetables remains technically and economically unfeasible due to their size, growth cycles, and space requirements. This limited crop range restricts the potential impact of VF and CEA on global food systems. Furthermore, consumer preferences and perceptions toward high-tech farming methods may vary, with some expressing skepticism over taste, nutritional value, or

"naturalness." Public education, product diversification, and research into new cultivars suitable for controlled environments are needed to broaden acceptance.

5. Legal and Regulatory Issues

VF and CEA systems often operate in a regulatory gray area, as existing agricultural, zoning, and food safety policies are not always designed to accommodate novel production methods. For example, building codes may restrict vertical installations, or water discharge regulations may not account for hydroponic effluent. Navigating these legal uncertainties can pose operational risks and deter investment. Developing clear, science-based regulatory frameworks that support innovation while ensuring environmental and public health safeguards is vital to mainstreaming these technologies.

Conclusion:

This chapter has examined the synergistic potential of Vertical Farming (VF) and Controlled Environment Agriculture (CEA) to address the growing challenges of global food security. It outlined the underlying principles, technologies, and operational mechanisms of both systems, and emphasized how their integration can yield higher productivity, enhanced resource efficiency, and resilience to environmental stressors. The analysis of real-world applications demonstrated their practical feasibility, especially in urban and climate-vulnerable regions. Case studies further illustrated their socioeconomic and ecological impacts, while the challenges section highlighted critical barriers to broader adoption, including high capital costs and limited crop diversity. The future prospects explored the alignment of these technologies with global sustainability goals and smart city development.

VF and CEA represent a paradigm shift in agriculture by enabling year-round food production that is independent of external climate and land constraints. Their strategic importance lies in their capacity to reduce reliance on imports, shorten supply chains, and bolster local food sovereignty. These systems contribute to a more distributed and adaptive food network that can better withstand disruptions from pandemics, geopolitical conflicts, or natural disasters. They also align closely with environmental goals by minimizing pesticide use, reducing water consumption, and promoting renewable energy adoption. Thus, integrating VF and CEA into national and global food strategies is essential to ensuring long-term nutritional security, economic stability, and ecological balance.

The advancement of VF and CEA requires an inclusive innovation ecosystem that integrates multidisciplinary research, public policy support, and private sector investment. Future progress depends on lowering technological and financial barriers, expanding crop varieties, and enhancing energy sustainability through innovations in AI, automation, and renewable energy systems. Education and capacity building will play a vital role in preparing a workforce equipped to operate and innovate within these systems. Furthermore, inclusive models that empower

smallholders, women, and marginalized communities can ensure equitable access to the benefits of these technologies. Moving forward, a collaborative, forward-looking approach that values sustainability, adaptability, and inclusivity will be critical to embedding VF and CEA within resilient, future-ready food systems.

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CUBOSOMES, A PROMISING CARRIER FOR ENCAPSULATION OF DRUG THERANOTIC APPLICATION

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Abstract:

Cubosomes are non-lamellar lipid structures with liquid crystalline layers. They have a structure like a "honeycomb" with bi-continuous domains of lipid and water, where surfactant assembles into bilayers and is twisted into a three- dimensional periodic surface, generating a densely packed structure. They have a distinct advantage over lamellar liposomes in that they have a large surface area that involves many internal segments, allowing for the effective trapping and continuous release of therapeutically active compounds also permit to incorporate highly lipophilic, hydrophilic, and amphiphilic drugs. This review article includes Introduction of cubosomes and few preparation techniques and their characterization and Evalution techniques, including as Particle Size Distribution (PSD), Small- Angle X-Ray Scattering, and Cryo- Transmission Electron Microscopy (Cryo-TEM), Entrapment efficiency, stability studies etc. along with few applications in pharmaceutical drug delivery using a cubosome as a vehicle.

Keywords: Cubosomes, Liquid crystalline layers, Liposomes, Cryo-Transmission Electron Microscopy.

1. Introduction

1.1 Definitions of Cubosomes

Between 1960 and 1985, Luzzati and Husson determined these honeycombed structures. Patton and Carey in 1979 described their observation in studies involving fat digestion, where simulated stomach contents combined with lipase and bilesalts resulted in dispersed particles of the bi-continuous cubic phase.[1] Larsson coined the term "Cubosomes," which refers to cubic molecular crystallography.[2] Cubosomes are discrete, sub-micron-sized nanostructured particles of the bi-continuous cubic liquid crystalline phase. They are made of polar and non- polar polymers, lipids, surfactants, and water which is why they are described as amphiphilic structures.

Being lyotropic liquid crystalline phases, bi-continuous cubic phases fall somewhere between solid crystals and isotropic liquids in terms of their qualities. These systems differ from

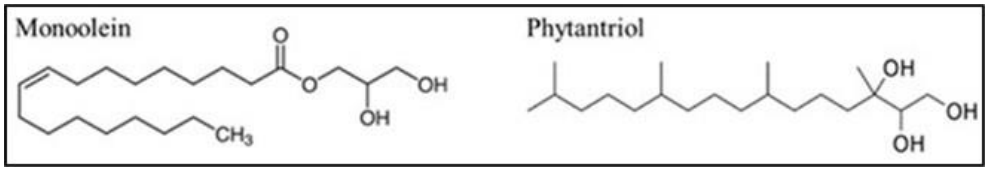
other systems in that they can maintain thermodynamic stability in the excess solvent, whereas other systems usually dissolve.[3] The cubosomes provide well-controlled delivery to pharmaceutical drug candidates, including anti- inflammatory agents, regional anesthetics, antibiotics, and cancer treatments. The cubosomal vaccinations with lipid entrapment were given as an adjuvant.[4]

1.2 Composition

1.2.1 Lipids- Amphiphilic lipids frequently used in cubosome manufacture are phytantriol and Glyceryl Monooleate, also referred as monoolein and PHYT. Lipids play a key role in the formation of cuboidal shaped vesicle.

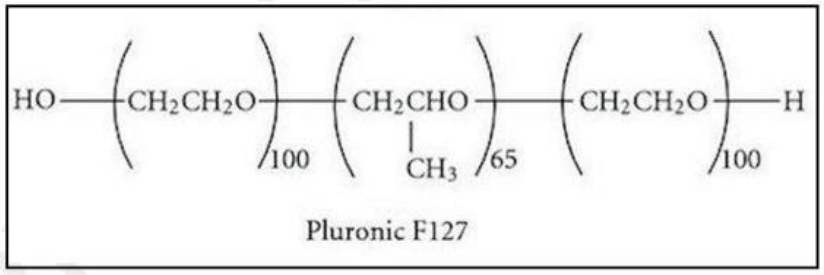
Glycerides of oleic acid and other fatty acids (monooleate) are combined to form monoolein, often referred to as glyceryl monooleate.[5] This amphiphilic molecule has an ester bond holding a hydrocarbon chain to the glycerol backbone. Every one of the three carbon locations on the glycerol backbone can support such a bond. This part of the monoolein molecule has hydrophilic/polar properties because the remaining two carbons have active hydroxyl groups that can form hydrogen bonds with water (headgroup). The hydrophobic properties of monoolein are conferred by the hydrocarbon chain (tail). Monoolein is a molecule of high interest due to its biocompatibility, biodegradability, non-toxicity, and capacity to create different liquid crystalline forms.[8][9][10]

Phytantriol is a biocompatible and well-known lipid, especially in the cosmetic industry. The molecule is composed of a highly branched phytanyl tail (hydrophobic section) and a tri-hydroxy headgroup (hydrophilic section). Phytantriol is a more stable alternative to monoolein because it lacks an ester functional group and is hence resistant to hydrolysis caused by esterase.[8][11][12]



1.2.2 Surfactant/stabilizer- Cubosomes require a surfactant to provide colloidal stability against re-coalescence to the bulk cubic phase. Pluronic's, particularly Pluronic F127, are the most often utilized stabilizing agents (F127). The three polymer blocks that make up the water-soluble stabilizer F127 are two polyethylene oxide (PEO) and one polypropylene oxide (PPO), arranged in a PEO-PPO-PEO configuration. In contrast to PPO, which is hydrophobic, PEO has a hydrophilic nature. The hydrophobic block is attached to the surface of the particles by this stabilizer, and the hydrophilic block forms a corona that sterically stabilizes the dispersion.

The most often used surfactant in cubosome preparation is Poloxamer 407 (P407), a PEO99- PPO67-PEO99 tri-block copolymer.[4] Its PPO parts are found either at the cubosome surface or inside the bilayer structure, while the PEO chains are exposed to the surrounding water phase. And D-α-tocopheryl poly (ethylene glycol)1000 succinate.



Cubosomes are self-assembled lipidic structures that can be found in three different morphologies:

Their sizes range from 50 nm to 500 nm. Each hydrophilic region's channel is connected three times by three in the Ia3d structure; four times by four in the Pn3m structure; and six times by six in the Im3m structure, where each water channel forms an orthogonal network.

1.3 Advantages

- Cubosomes are biocompatible, non-toxic, bioadhesive, non-immunogenic, and biodegradable due to their lipid composition.
- The preparation of cubosomes is simple.
- Substances that are hydrophobic, hydrophilic, or amphiphilic can be encapsulated within them.
- They have a high drug loading capacity due to their high internal surface area and cubic crystalline structures.
- Cubic phases of cubosomes can be dispersed to form long-lasting colloidal dispersions. Due to the comparatively insoluble nature of the cubic phase, cubosomes remain stable in excess water.
- Compared to other lipid carriers, cubosomes are effective solubilizers [6].
- Dosage frequency is reduced, thereby decreasing the overall cost of healthcare.
- Targeted and controlled release of bioactive substances is possible by using specific polymers.
- They can be formulated into transdermal skin patches due to their strong skin permeability.
- Due to their remarkable solubilizing properties, they are utilized in the treatment of skin, hair, and other bodily tissues.

1.4 Disadvantages

- Because there is a lot of water inside the cubosomes, there is minimal trapping of medications that are water-soluble.
- Its usage is restricted due to preservation issues, and drug leakage from preparation during shipment.
- Large-scale production can be challenging at times due to high viscosity

2. Method of Preparation

2.1 Top-down Approach: Cubosomes produced by the process are resistant to aggregation for up to a year. This approach includes two major steps show infigure

Step 1- The first step is the creation of the viscous bulk cubic phase, which is achieved by combining lipid with stabilizer to prevent aggregation;

Step 2- the second step is the application of high energy, such as high-pressure homogenization or sonication, leading to the formation of the cubosomes.[13]

Example- Sonication, Shearing, Homogenization, high pressure homogenization However, a few drawbacks are associated with this method such as a high amount of energy is required that can limit the incorporation of temperature-sensitive ingredients, especially peptides and proteins. the prerequisite formation of the viscose cubic structure, a drawback in large-scale production.[14]

2.2 Bottom-up Approach - Another way to make cubosomes at room temperature is by crystallizing them from precursors. This method is also known as the liquid precursor or solvent dilution method. Cubosomes are created by dispersing inverse micellar phase droplets in water at 80 degrees Celsius, then slowly cooling the solution to allow the droplets to crystallize into cubosomes.[15] The dispersion is a mixture comprising of liquid-crystal-forming lipid, polymer, and a hydro trope. The primary function of the hydrotrope is to dissolve lipids to produce liquid precursors while preventing the creation of a viscous liquid crystal phase at high concentrations.

Example -Vortex mixing, Stirring, solvent exchange method (solvent evaporation or nanoprecipitation).

In comparison between the two main approaches used for producing cubosomes, the dilution- based approach has some outstanding advantages over the top-down approach. Hence bottom-up approach is widely adopted technique in the cubosomes preparation.[16]

2.3 Fabrication Process- In a hot water bath at 60°C, Lipid and stabilizer were melted, and the required amount of drug was added. The mixture was continually stirred until it dissolved. Drops of distilled water are added while a vortex is set to homogenize the mixture. The optically isotropic cubic gel was created and allowed to remain at room temperature for up to 48 hours (about 2 days) before being disturbed by mechanical stirring and fractured by a probe sonication while at a cold temperature of 20°C in a water bath for 20 minutes.[17]

2.4 Spray Drying- Spray-drying produces encapsulated particles from an emulsion of liquid

droplets or a dispersion of solid particles in a concentrated aqueous polymer solution. A nozzle is used to spray the continuous and dispersed phases, forming suspension droplets that come into contact with a heated, dry air stream travelling in the opposite direction. Any extra water instantly evaporates, leaving behind dry powder particles made of the dispersed phase and encased in a shell made of the previously dissolved polymer. In a recent publication, cubosomes encapsulating the model antigen ovalbumin (OVA) was prepared using spray drying technique[18] and Cubosomes with surface cross-linked chitosan exhibit sustained release and bioavailability enhancement for vinpocetine.[19]

3. Cubosome Characterization and Evalution techniques

3.1 Electron Microscopy

The study of complicated fluid structures using cryogenic transmission electron microscopy (Cryo-TEM) enables a direct representation of cubosome size and form. Cubosomes and other vesicular systems preferred not to be examined in scanning electron microscope (SEM) because the formulation's integrity and robustness may be lost when it is exposed to an electron array.

3.2 Small Angle X-ray Scattering (SAXS)

An effective tool to determine the crystallographic structure of liquid crystalline phases is SAXS, which is frequently used to complement Cryo-TEM and other analytical techniques for liquid crystalline structure verification. X-rays interact with the electrons in the particles and are elastically dispersed in a SAXS experiment. SAXS recognizes periodic spatial configurations of various groups in any given direction.

Particle Size Distribution (PSD). The particle size distribution of the dispersions was determined using photon correlation spectroscopy. At regular time intervals, measurements were made at 250C utilizing the refractive index (RI) of cubosomes. Water was added to samples to dilute them and change the signal level. The average particle size (z-average) and poly dispersity index were determined.[30]

3.3 Entrapment Efficiency

Gel permeation chromatography or ultra filtering methods can be used to assess the cubosomes' drug loading and entrapment effectiveness. With the latter method, the concentration of the unentrapped medication is calculated and deducted from the total drug added. Using either an HPLC analysis or a UV spectrophotometer, the quantity of the medication is determined.[31]

3.4 Stability studies

Physical stability may be studied by studying organoleptic and morphological characteristics as a function of time. To determine potential alterations over time, particle size distribution and drug content can be measured at various time periods.[31]

4. Application of cubosomes

- Sustained drug release.
- Topical treatment of Burns.
- Melanoma therapy.
- Improved ophthalmic drug delivery.
- Carriers of cosmeceuticals actives.
- Theranostic applications.
- Delivery of protein vaccines.
- pH responsive drug delivery from cubic phase matrices.
- Protein entrapment and PEGylation of cubosomes.

Cubosomes as drug vehicles reported in recent years-

Conclusion:

Hence this non-lamellar lipid structures with liquid crystalline layers (Cubosomes) have an advantage over lamellar liposomes in that they contain a wide surface area with several interior segments, enabling the efficient trapping and ongoing release of therapeutically active substances. Hence are excellent tool for drug delivery systems due to the advantages such as the distinct structure of the cubic phase, its affinity to cellular membrane, and the biodegradability of lipids. Cubosomes have the potential to encapsulate hydrophilic, hydrophobic, and amphiphilic substances. They are also easy to manufacture and have all the characteristics, making them suitable for drug delivery systems in controlled transport applications.

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ADVANCES IN POLYMER CHEMISTRY: SYNTHESIS, PROPERTIES AND APPLICATIONS

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Abstract:

Polymer chemistry is a rapidly evolving field that has revolutionized various aspects of our lives. Polymers, being macromolecules composed of repeating units, exhibit unique properties that make them indispensable in various industries. This abstract provides an overview of the recent advances in polymer chemistry, highlighting the synthesis, properties, and applications of polymers.

The synthesis of polymers has witnessed significant advancements, with the development of novel polymerization techniques, such as controlled radical polymerization and ring-opening metathesis polymerization. These techniques have enabled the creation of polymers with tailored properties, such as molecular weight, architecture, and functionality.

The properties of polymers, including their mechanical, thermal, electrical, and optical properties, have been extensively studied. The development of new polymer architectures, such as dendrimers and nanocomposites, has led to the creation of materials with enhanced properties. Polymers have found numerous applications in various fields, including medicine, energy, electronics, and construction. Biodegradable polymers, such as polylactic acid and polyhydroxyalkanoates, have emerged as promising materials for biomedical applications. Conductive polymers, such as polyacetylene and polyaniline, have found applications in energy storage and conversion devices.

Introduction:

Polymer chemistry is a fascinating field that has led to the development of many innovative materials and technologies. Polymers are ubiquitous in nature and are also synthesized artificially for various applications. They have unique properties that make them useful in a wide range of fields, including materials science, engineering, medicine, and agriculture.

The study of polymers dates back to the early 19th century, when scientists such as Henri Braconnot and Christian Schönbein discovered that certain natural substances, such as cellulose and starch, could be broken down into simpler components. However, it wasn't until the early 20th century that the modern field of polymer chemistry began to take shape.

In the 1920s and 1930s, scientists such as Hermann Staudinger and Wallace Carothers made significant contributions to the field of polymer chemistry. Staudinger's work on the structure of polymers led to the development of the macromolecular hypothesis, which states that polymers are composed of long chains of repeating units. Carothers' work on the synthesis of polymers led to the development of nylon, one of the first commercially successful synthetic polymers.

Synthesis of Polymers

Polymers can be synthesized through various methods, including:

1. Addition Polymerization: This type of polymerization reaction involves the addition of monomers to a growing polymer chain. Examples include the polymerization of ethylene to form polyethylene.
2. Condensation Polymerization: This type of polymerization reaction involves the condensation of monomers to form a polymer, with the elimination of a small molecule such as water or methanol. Examples include the polymerization of nylon and polyester.
3. Ring-Opening Polymerization: This type of polymerization reaction involves the opening of a ring-shaped monomer to form a polymer. Examples include the polymerization of lactones and lactams.

Types of Polymers:

1. Natural Polymers

Natural polymers are polymers that occur naturally in the environment. Examples include:

- Cellulose: a polymer of glucose molecules found in plant cell walls
- Starch: a polymer of glucose molecules found in plant cells
- Proteins: polymers of amino acids found in living organisms
- DNA (Deoxyribonucleic acid): a polymer of nucleotides that contains genetic information
- Chitin: a polymer of N-acetyl glucosamine molecules found in the exoskeletons of insects and crustaceans

2. Synthetic Polymers

Synthetic polymers are polymers that are synthesized artificially. Examples include:

- Polyethylene: a polymer of ethylene molecules used in plastic bags and containers
- Polypropylene: a polymer of propylene molecules used in plastic containers and automotive parts
- Polyvinyl Chloride (PVC): a polymer of vinyl chloride molecules used in pipes, vinyl records, and window frames
- Nylon: a polymer of adipic acid and hexamethylene diamine molecules used in textiles and carpets

- Polyester: a polymer of ethylene glycol and terephthalic acid molecules used in textiles and plastic bottles

3. Biodegradable Polymers

Biodegradable polymers are polymers that can be broken down by living organisms. Examples include:

- Polylactic Acid (PLA): a polymer of lactic acid molecules used in biomedical applications and packaging
- Polyhydroxyalkanoates (PHA): a polymer of hydroxyalkanoic acid molecules used in biomedical applications and packaging
- Polybutylene Succinate (PBS): a polymer of butylene succinate molecules used in packaging and disposable cutlery
- Polybutylene Adipate-co-Butylene Terephthalate (PBAT): a polymer of butylene adipate and butylene terephthalate molecules used in packaging and disposable cutlery

4. Conductive Polymers

Conductive polymers are polymers that can conduct electricity. Examples include:

- Polyacetylene: a polymer of acetylene molecules used in electronic devices and sensors
- Polyaniline: a polymer of aniline molecules used in electronic devices and sensors
- Polythiophene: a polymer of thiophene molecules used in electronic devices and sensors
- Poly (3,4-ethylenedioxythiophene) (PEDOT): a polymer of ethylenedioxythiophene molecules used in electronic devices and sensors

5. Thermoplastic Polymers

Thermoplastic polymers are polymers that can be melted and reformed multiple times. Examples include:

- Polyethylene: a polymer of ethylene molecules used in plastic bags and containers
- Polypropylene: a polymer of propylene molecules used in plastic containers and automotive parts
- Polyvinyl Chloride (PVC): a polymer of vinyl chloride molecules used in pipes, vinyl records, and window frames
- Nylon: a polymer of adipic acid and hexamethylene diamine molecules used in textiles and carpets
- Polyester: a polymer of ethylene glycol and terephthalic acid molecules used in textiles and plastic bottles

6. Thermosetting Polymers

Thermosetting polymers are polymers that cannot be melted and reformed once they have been set. Examples include:

- Epoxy: a polymer of epoxide molecules used in adhesives, coatings, and composite materials
- Polyurethane: a polymer of urethane molecules used in foams, coatings, and adhesives
- Phenolic: a polymer of phenol molecules used in adhesives, coatings, and composite materials
- Melamine: a polymer of melamine molecules used in adhesives, coatings, and composite materials
- Silicone: a polymer of siloxane molecules used in sealants, adhesives, and coatings

7. Elastomeric Polymers

Elastomeric polymers are polymers that can stretch and recover their shape. Examples include:

- Natural Rubber: a polymer of isoprene molecules used in tires, gloves, and other rubber products
- Synthetic Rubber: a polymer of butadiene and styrene molecules used in tires, belts, and other rubber products
- Polyurethane: a polymer of urethane molecules used in foams, coatings, and adhesives
- Silicone: a polymer of siloxane molecules used in sealants, adhesives, and coatings

8. Biomedical Polymers

Biomedical polymers are polymers used in medical applications. Examples include:

- Poly(lactic-co-g

Properties of Polymers:

Mechanical Properties

1. Tensile Strength: The maximum stress a polymer can withstand without breaking.
2. Elastic Modulus: A measure of a polymer's stiffness and resistance to deformation.
3. Impact Resistance: A polymer's ability to withstand sudden impacts without breaking.
4. Hardness: A polymer's resistance to scratching and abrasion.

Thermal Properties

1. Melting Point: The temperature at which a polymer's crystalline structure melts.
2. Glass Transition Temperature: The temperature at which a polymer's amorphous regions become more mobile.
3. Thermal Conductivity: A polymer's ability to conduct heat.
4. Thermal Stability: A polymer's resistance to degradation at high temperatures.

Electrical Properties

1. Conductivity: A polymer's ability to conduct electricity.
2. Dielectric Constant: A measure of a polymer's ability to store electric charge.
3. Electrical Strength: A polymer's resistance to electrical breakdown.

4. Dielectric Loss: A measure of a polymer's energy loss due to electrical conduction.

Optical Properties

1. Transparency: A polymer's ability to transmit light.
2. Refractive Index: A measure of a polymer's ability to bend light.
3. Reflectivity: A polymer's ability to reflect light.
4. Absorbance: A polymer's ability to absorb light.

Chemical Properties

1. Chemical Resistance: A polymer's resistance to degradation by chemicals.
2. Solubility: A polymer's ability to dissolve in solvents.
3. Reactivity: A polymer's ability to react with other chemicals.
4. Stability: A polymer's resistance to degradation over time.

Rheological Properties

1. Viscosity: A polymer's resistance to flow.
2. Elasticity: A polymer's ability to return to its original shape after deformation.
3. Plasticity: A polymer's ability to undergo permanent deformation without breaking.
4. Creep: A polymer's gradual deformation over time under constant stress.

Biodegradable Properties

1. Biodegradability: A polymer's ability to break down naturally in the environment.
2. Compostability: A polymer's ability to break down in composting conditions.
3. Toxicity: A polymer's potential to harm living organisms.
4. Environmental Impact: A polymer's overall impact on the environment.

Applications of polymers related to polymer chemistry:

1. Packaging

- Plastic bags and containers: Polyethylene and polypropylene are commonly used.
- Bottles and caps: Polyethylene terephthalate (PET) and polypropylene are widely used.
- Food packaging: Polyvinyl chloride (PVC) and polyethylene are often used.

2. Textiles

- Clothing: Nylon, polyester, and polypropylene are commonly used.
- Carpets and upholstery: Nylon and polypropylene are widely used.
- Technical textiles: Polyethylene and polypropylene are used in applications such as geotextiles and medical textiles.

3. Construction

- Pipes and fittings: Polyvinyl chloride (PVC) and polyethylene are commonly used.
- Insulation: Polyisocyanurate (PIR) and polyurethane (PU) are widely used.
- Roofing and flooring: Polyvinyl chloride (PVC) and polyethylene are often used.

4. Electronics

- Wires and cables: Polyethylene and polypropylene are commonly used.
- Printed circuit boards: Polyimide and polyethylene are widely used.
- Electronic components: Polyethylene and polypropylene are often used.

5. Medicine

- Implants: Polyethylene and polypropylene are commonly used.
- Prosthetics: Polyethylene and polypropylene are widely used.
- Surgical instruments: Polyethylene and polypropylene are often used.

6. Aerospace

- Aircraft components: Polyimide and polyethylene are commonly used.
- Rocket components: Polyimide and polyethylene are widely used.
- Space suits: Polyethylene and polypropylene are often used.

7. Automotive

- Bumpers and dashboards: Polypropylene and polyethylene are commonly used.
- Interior components: Polypropylene and polyethylene are widely used.
- Exterior components: Polypropylene and polyethylene are often used.

8. Adhesives

- Pressure-sensitive adhesives: Polyacrylate and polyvinyl acetate are commonly used.
- Structural adhesives: Polyurethane and epoxy are widely used.
- Hot-melt adhesives: Polyethylene and polypropylene are often used.

9. Coatings

- Paints: Polyurethane and polyacrylate are commonly used.
- Varnishes: Polyurethane and polyacrylate are widely used.
- Coatings for metals: Polyurethane and epoxy are often used.

10. Biomedical Applications

- Tissue engineering: Polyethylene and polypropylene are commonly used.
- Drug delivery: Polyethylene and polypropylene are widely used.
- Biosensors: Polyethylene and polypropylene are often used.

Impact of Polymer Chemistry:

Economic Impact

1. Job Creation: The polymer industry is a significant employer, with millions of people working in polymer production, processing, and application.
2. GDP Contribution: The polymer industry contributes significantly to the GDP of many countries, with the global polymer market valued at over $1 trillion.
3. Innovation: Polymer chemistry has enabled the development of new products and technologies, driving innovation and economic growth.

Environmental Impact

1. Sustainability: Polymer chemistry has enabled the development of sustainable polymers, such as biodegradable and recyclable polymers, which can reduce plastic waste and minimize environmental impact.
2. Conservation of Resources: Polymer chemistry has enabled the development of polymers that can conserve resources, such as water and energy, by reducing the amount of materials needed for production.
3. Waste Reduction: Polymer chemistry has enabled the development of polymers that can reduce waste, such as biodegradable polymers that can break down naturally in the environment.

Social Impact

1. Improved Quality of Life: Polymer chemistry has enabled the development of products that have improved the quality of life for people around the world, such as medical devices, clothing, and packaging.
2. Healthcare: Polymer chemistry has enabled the development of medical devices and implants that have improved healthcare outcomes for millions of people.
3. Food Security: Polymer chemistry has enabled the development of packaging materials that have improved food security by reducing food waste and improving food safety.

Technological Impact

1. Advances in Materials Science: Polymer chemistry has enabled the development of new materials with unique properties, such as conductivity, strength, and durability.
2. Energy Applications: Polymer chemistry has enabled the development of polymers that can be used in energy applications, such as solar cells, fuel cells, and batteries.
3. Electronics: Polymer chemistry has enabled the development of polymers that can be used in electronic applications, such as displays, sensors, and actuators.

Medical Impact

1. Medical Devices: Polymer chemistry has enabled the development of medical devices, such as implants, prosthetics, and diagnostic equipment.
2. Drug Delivery: Polymer chemistry has enabled the development of polymers that can be used in drug delivery applications, such as controlled release and targeted delivery.
3. Tissue Engineering: Polymer chemistry has enabled the development of polymers that can be used in tissue engineering applications, such as scaffolds and matrices.

Aerospace Impact

1. Lightweight Materials: Polymer chemistry has enabled the development of lightweight materials that can be used in aerospace applications, such as aircraft and spacecraft.

2. High-Temperature Materials: Polymer chemistry has enabled the development of high-temperature materials that can be used in aerospace applications, such as rocket nozzles and heat shields.

3. Composites: Polymer chemistry has enabled the development of composites that can be used in aerospace applications, such as carbon fiber reinforced polymers (CFRP).

Conclusion:

Polymer chemistry is a vibrant and dynamic field that continues to evolve and expand into new areas. As researchers and scientists, it is essential to continue exploring the frontiers of polymer chemistry to develop novel materials and technologies that can address the complex challenges facing our world today. By advancing our understanding of polymer chemistry, we can create new opportunities for innovation and improve the quality of life for people around the world.

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UNDERSTANDING TRISOMY 13: FROM CHROMOSOMAL ANOMALIES TO MULTIDISCIPLINARY MANAGEMENT

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Abstract:

Patau syndrome, also known as Trisomy 13, is a rare but severe chromosomal disorder caused by the presence of an extra copy of chromosome 13 in all or some cells of the body. It is the third most common autosomal trisomy in live births and is associated with multiple congenital malformations affecting the brain, heart, face, and other organ systems. The condition presents with a broad spectrum of anomalies, including holoprosencephaly, cleft lip and palate, congenital heart defects, polydactyly, and genitourinary malformations. Most cases arise from meiotic nondisjunction, leading to full trisomy, although mosaic and partial forms also occur. The prognosis is extremely poor, with over 90% of affected infants dying within the first year of life. Management is challenging and often palliative in nature, focusing on improving quality of life and minimizing suffering. A multidisciplinary team approach involving pediatricians, geneticists, neonatologists, surgeons, and palliative care providers is essential for comprehensive care. Advances in prenatal screening and diagnosis have improved early detection, yet therapeutic interventions remain limited and largely supportive. While rare cases of prolonged survival have been reported, significant neurodevelopmental impairment persists in nearly all survivors. This review provides an overview of the genetic basis, clinical features, classification, pathophysiology, and management strategies for Patau syndrome.

Keywords: Trisomy 13; Patau Syndrome; Chromosomal Abnormalities; Congenital Malformations; Genetic Counseling; Neonatal Management

Introduction:

Patau syndrome, also referred to as trisomy 13, is a severe chromosomal disorder characterized by the presence of an extra copy of chromosome 13 in some or all of an individual's cells. This genetic anomaly results in significant disruption of normal embryonic development, leading to complex and multisystem congenital malformations. Although the clinical features of the condition were initially described by Thomas Bartholin in 1657, the chromosomal etiology was identified by Dr. Klaus Patau and Dr. Eeva Therman in 1960, after whom the syndrome is named [1]. Trisomy 13 is the third most frequently occurring autosomal trisomy in live-born infants, following trisomy 21 and trisomy 18. Its prevalence ranges from 1 in 7,000 to 1 in 29,000 live births, depending on the data source [1]. In certain familial contexts,

it may co-exist with other genetic disorders, such as Omenn syndrome, a rare immunodeficiency [2]. The prognosis for infants diagnosed with Patau syndrome remains extremely poor. The average survival duration is approximately nine months, and nearly 90% of affected infants do not survive beyond the first year of life [3]. This high mortality rate reflects the profound developmental instability caused by the additional chromosome. While normal development requires two copies of each autosome, the survival of embryos with three copies of chromosome 13 represents an exceptional case among autosomal trisomies. Trisomy 13 is considered the most severe autosomal imbalance compatible with life, and organs with intricate physiologic functions—particularly the central nervous system and the heart—appear highly vulnerable to such chromosomal anomalies due to disruptions in complex gene networks [4].The clinical presentation of Patau syndrome is marked by a broad spectrum of anatomical abnormalities. Common craniofacial findings include microcephaly, cleft lip and palate, midline facial defects such as cyclopia, microphthalmia or anophthalmia, and preauricular tags. Central nervous system anomalies, especially midline defects like alobar holoprosencephaly, are frequently observed. Cardiovascular defects are nearly universal and may include patent ductus arteriosus, ventricular septal defects, atrial septal defects, dextrocardia, and Tetralogy of Fallot. Limb deformities such as postaxial polydactyly, rocker-bottom feet, and congenital talipes equinovarus are also common. Additional organ systems affected include the lungs, liver, kidneys, gastrointestinal and genitourinary tracts, and pancreas. Notable anomalies in these systems include polycystic kidneys, hydronephrosis, horseshoe kidney, omphalocele, incomplete intestinal rotation, Meckel's diverticulum, cryptorchidism, hypospadias, labia minora hypoplasia, and bicornuate uterus. More than half of the affected individuals exhibit abnormalities in the genitourinary and renal systems, while gastrointestinal defects are present in fewer than half. Survivors often face severe psychomotor retardation, failure to thrive, profound intellectual disabilities, and seizures [5]. Management of Patau syndrome is challenging due to the consistently poor prognosis and the complexity of associated malformations. Intensive interventions are often debated and require careful ethical consideration. Newborns with facial deformities and airway compromise may require immediate oxygen supplementation, intubation, or tracheostomy. Congenital cardiac defects may necessitate surgical correction. Additional interventions such as cleft lip repair, gastrostomy tube placement, hernia repair, and orthopedic surgeries may be warranted based on individual clinical needs. Supportive care typically includes specialized nutritional feeds, seizure management, prophylactic antibiotics for urinary tract infections, and assistive devices such as hearing aids [3]. However, in most cases, the standard of care emphasizes palliative management, parental education, and the avoidance of invasive procedures to reduce suffering. The combination of high mortality and significant neurodevelopmental impairment poses a major challenge for families and healthcare professionals in making informed decisions about treatment options. Despite these challenges, recent studies indicate that early diagnosis,

individualized management, and selective therapeutic interventions may improve survival into early adolescence for a limited number of children. Nonetheless, these survivors continue to experience severe cognitive and developmental disabilities. This case and the associated management considerations have been reported in accordance with the SCARE 2020 Guidelines [6].

Classification

Patau syndrome, or trisomy 13, can be classified based on the genetic mechanism responsible for the presence of extra chromosome 13 material. The most common form is full trisomy 13, which accounts for approximately 75 to 85 percent of cases. In this type, every cell in the body contains a complete extra copy of chromosome 13. It typically results from nondisjunction during meiosis, leading to a uniform chromosomal abnormality in all cells. This form is associated with severe congenital anomalies and a very poor prognosis. Another variant is mosaic trisomy 13, observed in about 5 to 10 percent of cases. In mosaicism, only some cells have an extra chromosome 13, while others are chromosomally normal. This occurs due to a mitotic error after fertilization, leading to a mixture of normal and trisomic cells. Clinical presentation in mosaic trisomy 13 can be milder compared to full trisomy, and survival may be relatively longer, depending on the proportion and distribution of abnormal cells. Partial trisomy 13 represents a less common form, also seen in around 5 to 10 percent of cases. In this condition, only a segment of chromosome 13 is present in triplicate. It often results from a structural chromosomal rearrangement such as a Robertsonian translocation, where part of chromosome 13 is attached to another chromosome, typically chromosome 14 or 15. The severity of symptoms in partial trisomy 13 depends on the specific duplicated region and its size. This form may sometimes be inherited from a parent who carries a balanced translocation. A rare type involves the formation of an isochromosome. An isochromosome is an abnormal chromosome with two identical arms, resulting from the loss of one arm and duplication of the other. In the case of isochromosome 13, the duplicated material behaves similarly to a full trisomy, although this variant is infrequent.

Type	Mechanism	Frequency	Phenotype
Full Trisomy 13	Nondisjunction	75–85%	Severe
Mosaic Trisomy 13	Mitotic error post-fertilization	5–10%	Milder, variable severity
Partial Trisomy 13	Translocation	5–10%	Depends on duplicated region
Isochromosome 13	Chromosomal rearrangement	Rare	Similar to full trisomy 13

Epidemiology

Patau syndrome, or Trisomy 13, is a rare but clinically significant chromosomal disorder. It is the third most common autosomal trisomy in live-born infants, following Trisomy 21 (Down syndrome) and Trisomy 18 (Edwards syndrome). The estimated prevalence of Trisomy 13

ranges from approximately 1 in 7,000 to 1 in 29,000 live births, with variations depending on geographic region, maternal age distribution, and diagnostic practices. Higher maternal age, particularly over 35 years, is a recognized risk factor due to the increased likelihood of meiotic nondisjunction. Data from population-based studies, such as those conducted in England and Wales, indicate that the majority of cases—over 90%—are diagnosed prenatally through routine screening and confirmatory diagnostic techniques like chorionic villus sampling or amniocentesis. However, a significant proportion of affected pregnancies end in spontaneous abortion or elective termination due to the severity of the condition. Live births account for a small fraction of diagnosed cases, and the neonatal mortality rate is extremely high. Approximately 50% of affected infants die within the first month of life, and over 90% do not survive beyond the first year. The distribution of Patau syndrome types includes full trisomy 13 in approximately 75–85% of cases, mosaicism in 5–10%, and partial trisomy 13 (often due to Robertsonian translocations) in another 5–10%. The recurrence risk is generally low for sporadic cases caused by nondisjunction but may be higher in families with inherited chromosomal rearrangements. Due to its lethality and severity, Patau syndrome remains a rare and challenging condition in both prenatal and postnatal care settings [7].

History

Patau syndrome (trisomy 13) was first described clinically by Thomas Bartholin in 1657, and its chromosomal cause was identified by Klaus Patau and Eeva Therman in 1960, after whom the condition is named [13]. It arises from a third copy of chromosome 13 and results in severe developmental anomalies affecting the heart, central nervous system, and multiple organ systems. Data from England and Wales (2008–09) reported 172 diagnoses, with 91% identified prenatally. Outcomes included 111 terminations, 14 fetal losses, and 17 live births; adjusted estimates suggest around 18 live births [14]. Common anomalies involve the genitourinary tract, digestive system, pancreas, liver, kidneys, and lungs, along with major congenital heart defects such as double outlet right ventricle, atrioventricular septal defects, Tetralogy of Fallot, and ventricular septal defects [15]. Survival is poor, with most patients dying within the first year. However, recent Japanese studies indicate that intensive care and surgical intervention can extend survival up to approximately 733 days in selected cases [16]. While prenatal detection is possible, diagnostic accuracy varies. Standard ultrasound markers like the iliac angle may be less useful, though findings such as abnormal papillary muscle patterns can raise suspicion. However, prenatal diagnosis cannot predict postnatal severity or outcomes [17]

Signs and Symptoms

Patau syndrome (trisomy 13) often shows no noticeable symptoms during pregnancy. Initial suspicion may arise through prenatal screening such as cell-free DNA analysis, first-trimester combined screening, or findings on routine ultrasound. However, many cases are only confirmed after birth [18].After delivery, infants with trisomy 13 typically present with multiple

dysmorphic features and systemic abnormalities. Common signs include low birth weight, feeding difficulties, and hypotonia. Craniofacial anomalies are prominent, such as microcephaly, scalp defects (aplasia cutis), malformed ears, and capillary hemangiomas. Ocular anomalies such as microphthalmia, anophthalmia, and hypotelorism are also frequent [19]. Midline defects like cleft lip and/or palate are often observed, alongside postaxial polydactyly (extra fingers or toes). External genital abnormalities may include a small penis or enlarged clitoris. Neurological symptoms such as seizures and central apnea are common, and many infants exhibit hearing loss or complete deafness [20]. Approximately 80% of affected neonates have congenital heart defects, which may include ventricular septal defects, atrial septal defects, or more complex anomalies like Tetralogy of Fallot. Additionally, abnormalities in brain development (such as holoprosencephaly) and kidney malformations are frequently present [21].

Causes

Patau syndrome, or trisomy 13, is most commonly caused by a random chromosomal error that occurs during the formation of reproductive cells—either oocytes or spermatozoa. This error, known as nondisjunction, typically arises during meiosis, the process by which gametes are formed. As a result, an embryo inherits an additional copy of chromosome 13 in every cell, a condition referred to as full trisomy 13. In rare instances, the chromosomal error may occur after fertilization, during the early stages of cell division. This leads to a mosaic form of trisomy 13, in which only a portion of the body's cells carry the extra chromosome while the remainder are genetically normal. The clinical severity in mosaic cases can vary depending on the proportion and distribution of trisomic cells [22]. Advanced maternal age is a well-established risk factor, as the likelihood of meiotic nondisjunction increases significantly with maternal aging. Nevertheless, the majority of trisomy 13 cases are sporadic and not inherited. The recurrence risk for families is typically low when the cause is a de novo nondisjunction event. However, if trisomy 13 results from a structural chromosomal abnormality such as a balanced translocation—particularly one inherited from a parent—the recurrence risk may be considerably higher. In such cases, genetic counseling is strongly recommended to assess reproductive risks and options in future pregnancies [23,24].

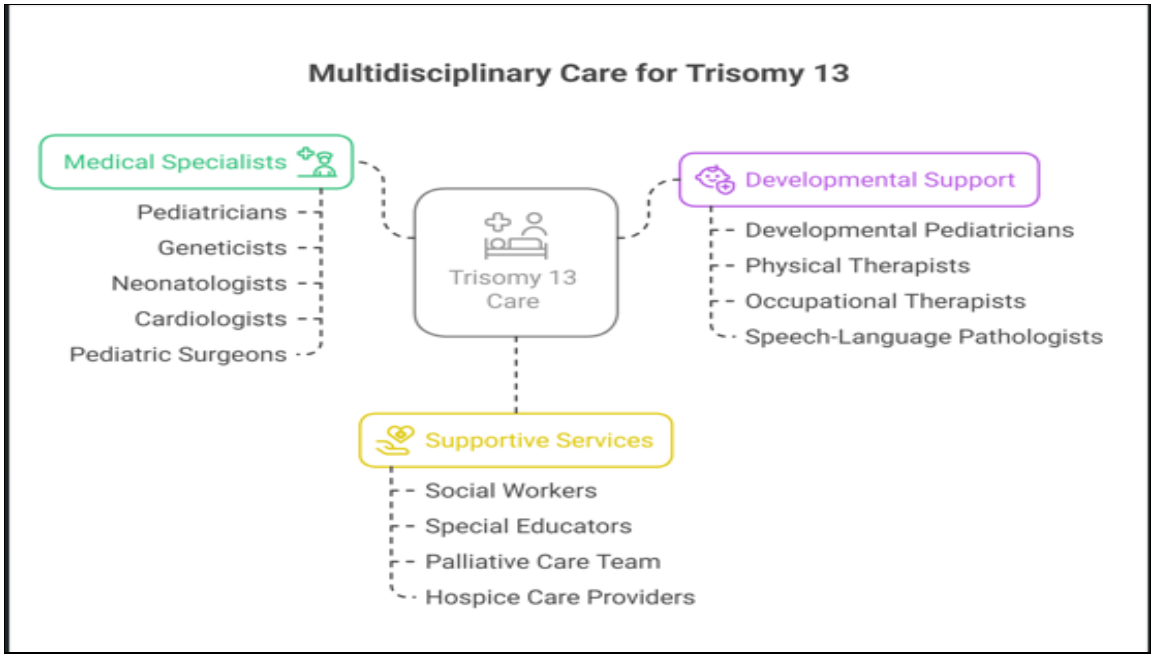
Pathophysiology of Patau Syndrome

Patau syndrome (trisomy 13) arises from a chromosomal abnormality during embryogenesis, most commonly due to meiotic nondisjunction. This error typically occurs during meiosis I, where homologous chromosomes fail to separate properly, resulting in a gamete with an extra chromosome 13. If fertilization occurs with such a gamete, the resulting zygote possesses three copies of chromosome 13. Approximately 91% of these nondisjunction errors originate from the maternal side [25]. In some cases, Patau syndrome may also result from a Robertsonian translocation involving chromosomes 13 and 14, where a break in the juxtacentromeric regions of two acrocentric chromosomes leads to an abnormal fused

chromosome. While this form may be inherited, most cases are sporadic. Mosaicism, where only a portion of the body's cells carry the extra chromosome, may also occur due to postzygotic errors [26]. The presence of an extra chromosome 13 disrupts embryonic development, particularly affecting highly organized systems such as the central nervous system and cardiovascular structures. This leads to severe congenital anomalies including holoprosencephaly, cardiac malformations, and craniofacial dysmorphisms. Although the mechanisms behind these effects are not completely understood, it is believed that the gene dosage imbalance interferes with critical signaling pathways during development [27]. While most autosomal trisomies are incompatible with life, trisomy 13 is one of the few that may result in a live birth. However, the phenotypic consequences are often profound, and survival beyond infancy remains rare in most cases [27].

Treatment

Medical care for a child diagnosed with Trisomy 13, also known as Patau syndrome, typically involves a multidisciplinary team approach due to the condition's complexity and multisystem involvement. A wide range of healthcare professionals may be involved to address the child's medical, developmental, and supportive care needs.



1. **Pediatricians**

   These primary care physicians specialize in the overall health of infants, children, and adolescents. They coordinate general medical care, monitor development, and act as the main point of contact for families.

2. **Geneticists**

   Genetic specialists assist in the diagnosis and management of genetic disorders. They provide genetic counseling to help families understand the condition, its inheritance patterns, and implications for future pregnancies.

3. **Neonatologists**

   These specialists in newborn care are involved immediately after birth, particularly in neonatal intensive care units. They manage complications that arise in newborns, such as respiratory issues and feeding difficulties.

4. **Cardiologists**

   Since congenital heart defects are common in Trisomy 13, cardiologists play a key role in diagnosing and managing cardiovascular abnormalities. They may recommend medical treatments or surgical interventions based on the severity of the condition.

5. **Pediatric Surgeons**

   Some children with Trisomy 13 may require surgical correction of structural anomalies such as cleft lip, cleft palate, or abdominal wall defects. Pediatric surgeons assess and carry out these procedures when necessary.

6. **Developmental Pediatricians**

   These professionals assess developmental progress and provide interventions tailored to developmental delays in motor, cognitive, and social skills.

7. **Physical Therapists**

   They support children with motor delays by providing therapy aimed at improving strength, coordination, posture, and mobility to enhance physical functioning and independence.

8. **Occupational Therapists**

   They focus on developing fine motor skills and daily living abilities, such as feeding, dressing, and grooming. Therapy may also include support for sensory processing challenges.

9. **Speech-Language Pathologists**

   These professionals work with children who have communication difficulties or feeding and swallowing issues. Their interventions support the development of expressive and receptive language and safe feeding techniques.

10. **Social Workers**

    Social workers provide emotional support and help families access resources, including financial assistance, healthcare services, and community programs. They are instrumental in guiding families through the complexities of long-term care.

11. **Special Educators**

    They design and implement individualized educational plans that address the specific learning needs of children with disabilities. Collaboration with families and schools ensures the child receives appropriate academic support and accommodations.

12. Palliative Care Team

This team focuses on improving quality of life by managing symptoms, addressing pain, and providing psychological and spiritual support. They also help families with care planning, especially when the prognosis is uncertain or limited.

13. Hospice Care Providers

When life-prolonging treatments are no longer effective or desired, hospice providers deliver compassionate end-of-life care aimed at comfort, dignity, and emotional support for the child and family.

Discussion:

Patau syndrome is among the most severe autosomal trisomies compatible with live birth. Characterized by an extra chromosome 13, its incidence varies between 1 in 7,000 and 1 in 29,000 live births. While historically identified over 350 years ago, its chromosomal basis was elucidated in 1960 by Klaus Patau. The pathogenesis is primarily due to meiotic nondisjunction, though mosaicism and structural rearrangements like Robertsonian translocations also contribute. The resulting gene dosage imbalance disrupts embryonic signaling pathways, particularly those essential for central nervous system and cardiac development. Clinically, Trisomy 13 is associated with a wide range of anomalies: holoprosencephaly, cleft palate, polydactyly, and severe congenital heart defects are hallmark features. In addition to visible anomalies, genitourinary, gastrointestinal, and musculoskeletal defects significantly impair viability and postnatal function. Classification into full, mosaic, and partial forms reflects variation in severity and life expectancy. Full trisomy, the most common, is universally fatal within the first year. Mosaic and partial forms may result in extended survival but often still entail profound neurodevelopmental impairment. Management remains ethically complex. Most cases are identified prenatally, and many pregnancies are electively terminated. For live-born infants, decisions about aggressive intervention versus palliative care must consider not only clinical factors but also parental values and quality of life considerations. Multidisciplinary teams are essential in guiding families through genetic counseling, supportive therapies, and, where feasible, surgical correction of life-threatening anomalies. Recent case reports indicate that some children, particularly those with mosaic forms, may survive beyond infancy with supportive care and selected surgical interventions. However, meaningful cognitive and motor development is rarely achieved. Future directions include improved prenatal screening, molecular diagnostics, and more nuanced decision-making models to align care with family preferences and evolving ethical standards in neonatal medicine.

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INTEGRATION OF MATHEMATICAL AND COMPUTATIONAL SCIENCES

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Abstract:

Mathematical science is the biggest Branch of Science which is closely related with all other science subjects like Physics, Chemistry, data Science and Computer Science**.** Mathematical and computational science is an interdisciplinary field that combines mathematical theory and computational techniques to solve complex problems across various disciplines. It focuses on developing and applying mathematical models and computational tools to understand and solve problems in fields like physics, engineering, finance, and data science. mathematical and computational science equips individuals with the skills and knowledge to tackle complex problems by leveraging the power of mathematics and computation. It also prepares Students to solve complex interdisciplinary problems by applying mathematical and computational tools. The Major offers a unique blend of courses in theory and modern applications of Mathematics and Computational Sciences. The objective is to create graduates with a deep understanding of the fundamental principles of mathematics who can apply strong computational techniques to model and solve problems in Physics, Economics, Finance, Engineering, and other domains. This Paper includes Relation between Mathematical and computational Sciences, Specific areas within mathematical and computational science and Career opportunities and.

Introduction:

Mathematical Science is the study of quantity, structure, space, and change, evolving from fundamental practices like counting and measuring. It's a science that uses logical reasoning and quantitative computation to solve problems, encompassing various fields like natural sciences, engineering, and social sciences. It's not about a single discovery, but a continuous evolution from basic practices to complex theories and applications.

Computational science, also known as scientific computing, is a field that uses computational techniques to solve complex scientific problems. It combines computer science, mathematics, and domain-specific knowledge (like physics, biology, or engineering) to develop and apply computational models and simulations to understand and analyze complex systems. Essentially, it provides a third approach to scientific inquiry, alongside theory and experimentation.

Mathematical and computational science bridges the gap between theoretical mathematics and practical applications by using computer science and numerical methods to

address scientific, engineering, and other challenges. is a field that leverages mathematical principles and computational tools to analyze, model, and solve complex problems across various disciplines. mathematical and computational science provides a powerful framework for understanding and solving complex problems by integrating mathematical theory with computational tools and techniques.

- **Relation Between Mathematical and computational Sciences:**

Mathematical and computational sciences are closely intertwined, with mathematics providing the theoretical foundation and computational science enabling the practical application of mathematical principles, especially through algorithms and computer simulations. Mathematics offers the tools for modeling and analysis, while computational science provides the means to execute those models and explore complex systems through computation.

- **Computational science bridges the gap to practical application**:
  - **Algorithms and Programming:**

Computational science focuses on developing algorithms and programming techniques to translate mathematical models into executable code for computers.

  - **Simulation and Modeling:**

Computational science enables the creation of virtual laboratories through computer simulations to study complex systems and phenomena.

  - **Data Analysis:**

Computational methods are used to analyze the vast amounts of data generated by simulations and experiments.

- **Mathematics provides the theoretical framework:**
  - **Abstract Concepts:**

Mathematics provides the abstract concepts, theorems, and logical structures that underpin computational models.

  - **Modeling:**

Mathematical models are used to represent real-world phenomena in a way that can be analyzed and simulated.

  - **Analysis:**

Mathematical tools like calculus, linear algebra, and statistics are essential for analyzing the data generated by computational models.

- **Examples of their Interplay**:
  - **Algorithm Design:**

Mathematics, especially discrete mathematics and graph theory, provides the foundation for designing efficient algorithms, which are crucial in computer science.

- **Artificial Intelligence:**

AI and machine learning rely heavily on mathematical concepts like linear algebra, calculus, and statistics, while computational techniques are used to train and deploy these models.

- **Computer Graphics:**

Geometric modeling, linear algebra, and calculus are essential for creating realistic computer graphics and simulations.

- **Cryptography:**

Number theory and abstract algebra are fundamental to cryptography, while computational methods are used to implement and break encryption algorithms.

- **Computational Biology:**

Mathematical models of biological systems are translated into computer simulations to study complex biological processes.

Totally mathematics provides the language and tools, while computational science provides the means to speak that language and build with those tools to solve complex problems in various fields.

- **Specific areas within mathematical and computational science**

- **Computer Science:**

  Mathematics and computer science are closely related to each other.This field deals with the theory and practice of computation, including the design and development of hardware and software systems.

- **Pure Mathematics:**

  This foundational area explores abstract mathematical concepts and theories, such as algebra, analysis, and topology, which often serve as the basis for other areas.

- **Applied Mathematics:**

  This field focuses on the applications that is by using mathematical methods to solve practical problems in various scientific and engineering domains.

- **Statistics:**

  This involves the study of data collection, analysis, interpretation, presentation, and organization, with applications in diverse fields like social sciences, medicine, and finance.

- **Graph Theory:**

  This field studies the properties and applications of graphs, which are mathematical structures used to represent relationships between objects, with applications in social networks, computer networks, and more.

- **Combinatorial Network Theory:**
  This area deals with the study of discrete structures and their properties, with applications in computer science, cryptography, Electronics, Networks and other fields.
- **Numerical Analysis:**
  This area focuses on developing and analyzing algorithms for solving mathematical problems that are often computationally intensive, such as those arising in physics, engineering, and finance.
- **Optimization:**
  This field is concerned with finding the best solution from a set of feasible options, with applications in areas like logistics, resource allocation, and machine learning.

- **Career opportunities**

There are a lot of career opportunities in mathematical and computational science. career opportunities are booming due to the increasing reliance on data and computation across various industries. A BTech in Mathematics and Computing equips graduates for roles in AI/ML, data science, finance, cyber security, and software development. The field offers diverse opportunities, from research and academia to industry applications in finance, technology, and healthcare.

- **Data Science and Analytics :**
  - **Data Scientist**
    Analyzes large datasets to extract insights, build predictive models, and support data-driven decision-making.
  - **Data Engineer**
    Designs and implements data pipelines, manages data storage, and ensures data quality for analysis.
  - **Business Intelligence Analyst**
    Uses data visualization and reporting tools to provide business insights.
  - **Machine Learning Engineer**
    Develops and deploys machine learning models for various applications, such as image recognition, natural language processing, and recommendation systems.
- **Finance and Fintech**
  - **Quantitative Analyst (Quant)**
    Develops and implements mathematical models for financial markets, risk management, and algorithmic trading.
  - **Financial Engineer**
    Combines mathematical and computational techniques to design and analyze financial products and strategies

- **Actuary**
  Assesses and manages financial risk, particularly in insurance and pensions.

❖ **Research and Academics**

- **Computational Scientist**
  Applies computational methods to solve complex problems in various scientific fields, such as physics, biology, and engineering.
- **Research Analyst**
  Conducts research using mathematical and computational techniques to advance knowledge in specific fields.
- **Professor/Lecturer**
  Teaches and conducts research in mathematics, computer science, or related fields.

❖ **Other Emerging Fields**

- **Computational Biology/Bioinformatics:** Uses computational methods to analyze biological data, such as genomics and proteomics.
- **Computational Neuroscience:** Studies the brain and nervous system using computational models and simulations.
- **Climate Modeling:** Develops mathematical models to simulate and predict climate change.

Conclusion:

Totally the fields of mathematical and computational sciences are rapidly advancing, driven by the synergy between mathematical theory and computational power. Mathematics provides the theoretical framework, while computational science provides the tools to implement and test these theories, leading to significant advancements in various fields. This interdisciplinary approach is crucial for solving complex problems across various domains, including artificial intelligence, quantum computing, and big data analytics. The ability to model, simulate, and analyze intricate systems using computational methods is transforming scientific research, engineering design, and many other fields.

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PURINE AND POLYKETIDE DERIVED PSEUDOALKALOIDS: CHEMISTRY AND PHARMACOLOGY

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Introduction:

Pseudoalkaloids represent a specialized category of naturally occurring compounds that differ fundamentally from true alkaloids in their biosynthetic origin. While true alkaloids are synthesized directly from amino acid precursors, pseudoalkaloids are not derived from amino acids. Instead, their carbon backbones originate from a variety of non-amino acid sources, such as terpenoids, steroids, polyketides, or purine derivatives. The incorporation of nitrogen into these structures generally occurs at a later stage of biosynthesis, typically through processes such as amination or transamination. This characteristic pathway sets pseudoalkaloids apart from the traditional biosynthetic routes observed in true alkaloids and contributes to their diverse structural and functional properties [Gandhinagar (2022)].

Classification of Pseudoalkaloids

Pseudoalkaloids are broadly classified based on the nature of their carbon skeletons and the biosynthetic precursors involved in their formation. The main categories include:

1. Terpene-Derived Pseudoalkaloids: These pseudoalkaloids are formed from terpenoid structures, which are built from isoprene units. A prominent example is aconitine, a highly toxic diterpenoid pseudoalkaloid obtained from species of the Aconitum genus. Aconitine is known for its powerful neurotoxic and cardiotoxic effects, historically used in traditional medicine in very controlled doses for pain relief but also notorious for its toxicity when misused. Such compounds highlight the dual nature of pseudoalkaloids as both therapeutic and toxic agents [Zhao ***et al.*** (2024); Aniszewski (2007)].

2. Sesquiterpene-Derived Pseudoalkaloids: Derived from sesquiterpenes (15-carbon terpenoid units), these compounds incorporate nitrogen through enzymatic modifications during their biosynthesis. Examples include evonoline, cassine, and aristolochic acid, which are typically

found in plants and some fungi. These pseudoalkaloids often possess potent biological activities such as insecticidal, cytotoxic, or neurotoxic properties, making them of interest in both pharmacological research and agricultural pest control [Dong *et al.* (2024); Manase *et al.* (2023)].

3. Steroid-Derived Pseudoalkaloids: These compounds arise from steroidal or sterol precursors, such as cholesterol. Notable examples include solanine and solanidine, which are glycoalkaloids primarily found in members of the Solanaceae family, such as potatoes and tomatoes. These pseudoalkaloids act as natural defense compounds in plants, offering protection against herbivores and microbial infections. While toxic in high concentrations, they have also been studied for potential pharmacological applications, including anticancer and antimicrobial effects [Dong *et al.* (2024); Manase *et al.* (2023)].

Purine-Derived Pseudoalkaloids: This subclass includes compounds formed from purine bases such as adenine or guanine. The most recognized members are caffeine, theobromine, and theophylline—naturally occurring methylxanthines commonly found in beverages like tea, coffee, and cocoa. These compounds exert stimulant effects on the central nervous system, increase alertness, and have mild diuretic and bronchodilatory properties. They are widely used both as natural stimulants and as active ingredients in pharmaceutical formulations for respiratory conditions such as asthma [Yang *et al.* (2022)].

5. Polyketide-Derived Pseudoalkaloids: These pseudoalkaloids are biosynthesized from polyketide chains, which are assembled by successive condensation of acetate or propionate units. Nitrogen is introduced during later biosynthetic steps, yielding complex nitrogenous compounds. A well-known example is mycophenolic acid, a secondary metabolite produced by certain fungi, particularly Penicillium species. It exhibits potent immunosuppressive activity and is used clinically to prevent organ transplant rejection [Hansen *et al.* (2011)].

Purine Derived Pseudoalkaloids

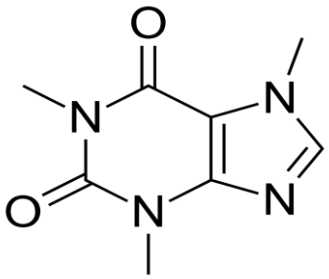
Purines consist of two connected rings from pyrimidine and imidazole systems resulting in these compounds. The biosynthesis of these compounds starts from adenine or guanine before they undergo structural changes resulting in different biological activities. Caffeine and theobromine behave as CNS stimulants due to their capability to bind adenosine receptors.

Caffeine

Caffeine is a natural stimulant most commonly found in coffee, tea, cocoa, and energy drinks. It works primarily by stimulating the central nervous system, helping to increase alertness and reduce fatigue. Chemically, it is classified as a methylxanthine and exerts its effects mainly by blocking adenosine receptors in the brain, which helps delay feelings of drowsiness. Caffeine is widely consumed around the world for its energizing effects and is also used in some medications to enhance pain relief or treat drowsiness [Vallombroso (2004)].

Chemistry

Pure anhydrous caffeine is a white, odorless powder with a bitter taste and a melting point of 235–238 °C. It has moderate solubility in water at room temperature (2g/100 mL) but dissolves rapidly in boiling water (66 g/100 mL). Additionally, it is moderately soluble in ethanol (1.5 g/100 mL). Caffeine is weakly basic, with a conjugate acid pKa of approximately 0.6, requiring a strong acid for protonation. It lacks stereogenic centers and is therefore classified as an achiral molecule [Vallombroso (2004); Feba *et al.* (2023)].



Caffeine's xanthine core consists of two fused rings: a pyrimidinedione and an imidazole. The pyrimidinedione ring contains two amide functional groups that primarily exist in a zwitterionic resonance, where nitrogen atoms form double bonds with adjacent amide carbon atoms. Consequently, all six atoms in the pyrimidinedione ring system are sp^2 hybridized and planar. The imidazole ring also exhibits resonance. As a result, the fused 5,6 ring core of caffeine has a total of ten π-electrons, making it aromatic according to Hückel's rule [Feba *et al.* (2023)].

Pharmacology

Antioxidative Property: Caffeine functions as an antioxidant through mechanisms that eliminate reactive oxygen species (ROS) while binding metal ions and strengthening antioxidant resistance in the body. The science supports caffeine's capability to remove hydroxyl radicals through electron paramagnetic resonance spectroscopy tests. The presence of caffeine helps chelate copper ions to prevent oxidative damage in the body. Marked increases in caffeine dosage can induce pro-oxidant effects but the substance enhances the activities of antioxidant enzymes superoxide dismutase and catalase [Choi *et al.* (2010)].

Antidiabetic Property: Medical experts study how caffeine helps diabetes patients through enhanced insulin sensitivity and improved glucose metabolic activities. Scientific studies show that people who consume more caffeine experience less chance of developing type 2 diabetes. Doctors have observed enhanced insulin secretions in diabetic rats and humans who used caffeine possibly because the stimulus increases pancreatic beta cell cAMP levels. Research shows that caffeine's metabolic outcomes remain intricate thus demanding careful evaluation in medical applications [Alperet *et al.* (2020)].

Antiproliferative Effect: The inhibition of phosphodiesterase (PDE) by caffeine lets cAMP levels expand to slow down cell cycle processes and trigger programmed cell death. Normal

cellular growth processes initiated by adenosine become disrupted because the substance hinders adenosine-mediated cell growth while blocking tumor cell proliferation. Scientists demonstrate that caffeine interferes with liver cancer growth through the AMPK pathway and functions as a protective agent against gastrointestinal and liver cancers through protein downregulation [Romualdo *et al.* (2019)].

Cardiovascular Effects: When consumed caffeine triggers a surge in blood pressure by releasing catecholamine hormones into the system. The substance modulates blood vessel responses because its action can either produce vessel relaxation or tightness during specific situations. A daily consumption of 2–3 cups of caffeine provides heart benefits together with benefits for diabetes and atherosclerosis while remaining generally safe to consume. The consumption of too much caffeine including energy drinks should be avoided [Voskoboinik *et al.* (2019)].

Orthopedic Effects: Excessive consumption of caffeine leads to decreased calcium absorption, which affects bone health and raises the risk of osteoporosis primarily among women in menopause. Long-term coffee intake is associated with decreased bone density and increases fracture risks. Caffeine performs an enhancing function for pain relief along with muscle endurance characteristics in sports medicine together with rehabilitation scenarios [Guillán-Fresco *et al.* (2020)].

Neurodegenerative Diseases: Research shows caffeine provides protective benefits to the nervous system which decreases the probability of developing Alzheimer's or Parkinson's diseases. The inhibition of beta and gamma secretase enzymes together with the prevention of β-amyloid aggregation cause decreased β-amyloid levels that can potentially treat Alzheimer's disease. Parkinson's patients benefit from caffeine's ability to stop adenosine A2A receptors while simultaneously preserving dopamine amounts and delaying symptoms of motor decline. Research shows that caffeine can cancel out the neurotoxicity caused by anti-seizure drugs prescribed to newborns [Zhou and Zhang (2021)].

Metabolic Effects: After blocking hypothalamic adenosine receptors, caffeine helps people lose weight through energy metabolism increase and appetite reduction. Research demonstrates caffeine has potential to treat NAFLD along with other obesity-linked conditions because it improves fatty acid breakdown and blocks fat synthesis. The effect of caffeine on glucose levels in diabetics remains unclear so additional studies for safe use are necessary [Paiva *et al.* (2022)].

Hepatoprotective Effects: The consumption of caffeine seems to reduce liver fat accumulation which lowers the chances of developing NAFLD. The liver protection mechanism which the substance provides stems from its combination of anti-inflammatory antioxidants that reduce both oxidative stress and inflammatory molecules. Research indicates that consuming caffeine acts both as a preventive measure against liver fibrosis and supports liver conditions by

controlling enzyme activity during treatment of alcoholic diseases and chronic conditions [Papandreou and Andreou (2015)].

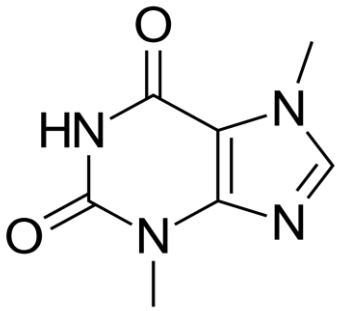
Wound Healing: The natural healing process of wounds receives a speed boost from caffeine because it enhances fibroblast activity combined with collagen production which leads to tissue restoration. This substance promotes an environment suitable for healing through its anti-inflammatory capabilities. The combination of analgesic with vasoconstrictive effects in caffeine creates improved blood circulation to wounds by enhancing microcirculation [Namviriyachote *et al.* (2019)].

Theobromine

Theobromine is a natural compound found primarily in cocoa beans, and thus in chocolate products. It belongs to the methylxanthine class of chemicals, closely related to caffeine, but has milder stimulant effects. Theobromine acts as a vasodilator, diuretic, and heart stimulant, and contributes to the mood-lifting effects of chocolate. Unlike caffeine, it does not strongly affect the central nervous system, making it less likely to cause jitteriness. It is also toxic to some animals, like dogs and cats, because they metabolize it slowly [Dock (1926)].

Chemistry

Theobromine exists as white crystalline powder with 295 °C as its melting point. Theobromine shows moderate dissolving ability in water at 0.67 g/100 mL but complete solubility occurs when combined with organic solvents including ethanol and chloroform. Theobromine shows basic properties through its pKa value of 7.9 due to its weak basic nature.



Theobromine exists as 3,7-dimethylxanthine and contains the xanthine basic core which has methyl groups at positions 3 and 7 on its purine framework. Xanthine contains two fused heterocyclic rings including a pyrimidinedione ring linked with an imidazole ring which shows similar patterns to caffeine but different methylation patterns. Resonance stabilization characterizes theobromine because its nitrogen atoms form π bonds that function through ring structures to satisfy Hückel's rule for an aromatic system of ten π electrons [Dock (1926)].

Pharmacology

Cardiovascular Effect: Theobromine functions as a bronchodilator and vasodilator while stimulating the heart moderately although its potency falls between theophylline and caffeine.

The cardiovascular effects of theobromine have been reported in anecdotal studies. Medical practitioners administer it to manage angina pectoris symptoms based on its reported vasodilatory capacity. Scientific reports continue to dispute whether polyphenols contained in cocoa dominate the effects on cardiovascular health. Research indicates this substance blocks the activity of PARP-1 while also playing a role in vascular dysfunction and associated inflammation. More research needs to be done to determine if cocoa has positive effects on cardiovascular health [Baron *et al.* (1999); Geraets *et al.* (2006)].

Respiratory Effect: Clinical research indicates that theobromine helps bronchodilation control asthma symptoms in patients yet it works less effectively than theophylline. Research has shown theobromine can suppress cough reactions by limiting the activity of the vagus nerve better than codeine without any unwanted side effects. The tobacco industry adopts cocoa powder to boost nicotine absorption because of theobromine's capacity to dilate bronchioles. The specific biological functions remain unclear but adenosine receptor antagonism and alternative pathways may explain its mechanism [Brown *et al.* (2008)].

Renal Effect: Similar to theophylline and caffeine theobromine functions as a non-selective adenosine receptor antagonist although its diuretic properties remain weaker than both compounds. Theobromine absence of boosted calcium and sodium excretion in urine distinguishes it from the effects of caffeine. Research contradicts previous findings that theobromine provides stronger renal effects than caffeine by revealing no significant variations in urine volume after ingestion [Fredholm and Lindström (1999)].

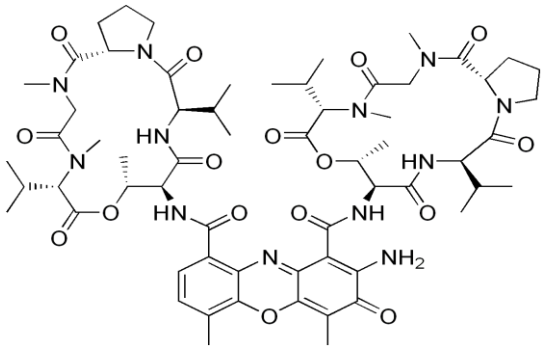
Dental Effect: The sugary composition of chocolate seems to contribute to dental caries prevention. Studies indicate that theobromine performs better than fluoride in enamel strengthening while simultaneously preventing plaque development [145, 146]. Coupled with polyphenols cocoa extracts prove effective against tooth decay [147]. Data suggests that caffeine triggers equivalent reactions to methylxanthines but polyphenols function through different pathways so combining these substances could potentially result in better effectiveness [Sadeghpour (2007); Percival *et al.* (2006)].

Polyketide Derived Pseudoalkaloids

Different enzymes produce these pseudoalkaloid compounds by adding nitrogen to polyketides derived from acetate as their starting material. Beta-ketoacyl structural units in polyketides lead to elaborate chemical ring formations. Actinomycin D stands as an outstanding example of the natural process where polyketide frameworks incorporate nitrogen molecules to create heterocyclic products. The antibiotic and toxic characteristics of these pseudoalkaloids develop from their highly functionalized structures.

Actinomycin D (Dactinomycin)

Actinomycin D, also known as Dactinomycin, is a chemotherapy drug used to treat various types of cancer, including Wilms' tumor, rhabdomyosarcoma, and gestational trophoblastic neoplasia. It is a cytotoxic antibiotic derived from Streptomyces bacteria and works by intercalating into DNA, thereby inhibiting RNA synthesis and cell replication. Because of its strong anti-tumor properties, Actinomycin D is commonly used in combination chemotherapy regimens. However, it can cause significant side effects such as nausea, hair loss, and bone marrow suppression [ChemSrc (2025)].



Chemistry

Actinomycin D exists as a red powder with a molecular weight of 1255.42 g/mol, while showing a molecular formula of C62H86N12O16. This compound exists as a red powder that exhibits a melting point between 251-253°C and shows a predicted pKa value of approximately 8.94. Actinomycin D remains stable at temperatures between 2-8°C when dissolved in DMSO and ethanol solutions. The antibiotic contains a phenoxazinone chromophore that links to two pentapeptide lactone rings as its fundamental structure **[**ChemSrc (2025)]; ChemicalBook (2025)].

Pharmacology

Gestational Trophoblastic Disease Treatment: Actinomycin D (Dactinomycin) is an essential chemotherapeutic drug for treating patients with gestational trophoblastic disease (GTD) and its conditions. Medical experts administer Actinomycin D as the primary chemotherapy treatment for these medical conditions. Actinomycin D shows outstanding performance in eliminating abnormal trophoblastic cells, which prevents disease progression and associated medical complications. Clinical evidence shows that Actinomycin D demonstrates superior treatment outcomes as initial therapy in specific treatment settings, according to existing review evidence. Medical treatment of patients with metastatic GTD involves primary chemotherapy and widespread use of Actinomycin D in combination treatments to achieve effective results. Experts in medical fields advise using brain-area radiotherapy with chemotherapy for treating organ metastases. Actinomycin D treatment combined with chemotherapy accelerates menopausal onset in affected female patients during their lifetime [Kang *et al.* (2010); Lawrie *et al.* (2016)].

Wilms' Tumor Treatment: Actinomycin D (dactinomycin) functions as the primary chemotherapy medicine for Wilms' tumor patients because it leads to better outcomes when used alongside surgical treatments and radiology. Vincristine is used along with Actinomycin D to provide standard cancer treatment to Wilms' tumor patients. Surgical teams administer preoperative Actinomycin D and vincristine treatments under the UMBRELLA SIOP protocol to shrink tumors ahead of surgery. Doctors have achieved near 90% survival rates thanks to the multidimensional approach using Actinomycin D, which enables them to decrease treatment dosages without impacting patient success [Burgert and Glidewell (1967); Van Den Heuvel-eibrink *et al.* (2017)].

Rhabdomyosarcoma Treatment: Dactinomycin (Actinomycin D) is an essential component of vincristine, ifosfamide, and Actinomycin D (IVA) chemotherapy treatments. The combination of chemotherapy treatment courses leads to increased survival effects because RMS shows favorable responses to treatment in 80% of patients. Research shows that alveolar-type RMS patients had better survival rates using VAC chemotherapy with doxorubicin and cisplatin combination during their early stages, while stage III RMS of the bladder patients retained bladder tissue according to the IRS study III. Present treatment regimens incorporating Actinomycin D produce survival outcomes that reach 60 to 70 percent for RMS patients, thus demonstrating its vital role in RMS care, as research shows [Pappo *et al.* (1995); Dagher and Helman (1999)].

Ewing Sarcoma Treatment: The medicine Actinomycin D (dactinomycin) functions as a central component in multi-agent chemotherapy regimens for Ewing sarcoma and appears in VAC (vincristine, actinomycin D, cyclophosphamide) and VAI (vincristine, actinomycin D, ifosfamide) protocols. Actinomycin D functions as a primary drug agent for consolidation treatment after standard induction therapy. Actinomycin D treatment for patients follows 7-8 cycle protocols that span 5-6 months through either slow injections or 30-minute intravenous infusions. The absence of actinomycin D in treatment protocols allows the use of carboplatin which provides similar survivorship results during consolidation therapy according to current research[167]. The chemotherapy drug Actinomycin D features prominently in VAIA and other more aggressive treatment protocols for metastasized Ewing sarcoma where it leads to 51.2% objective response rates in adult patients [Özkan *et al.* (2022); Atallah *et al.* (2020)].

Conclusion:

Pseudoalkaloids represent a fascinating and structurally diverse class of nitrogenous natural products that diverge from traditional alkaloid biosynthesis. Their unique origin—often from terpenes, steroids, purines, or polyketides—underscores the biochemical ingenuity found in nature. These compounds are not only significant for their ecological roles in plant defense and microbial survival but also hold immense promise for pharmacological applications. From the neuroactive effects of caffeine and theobromine to the anticancer properties of actinomycin D,

pseudoalkaloids continue to shape therapeutic research and drug development. Their wide range of biological effects, coupled with complex biosynthetic pathways, warrants deeper scientific exploration, especially with advancements in metabolomics and synthetic biology. Future studies may uncover novel pseudoalkaloids with enhanced efficacy and safety profiles, offering new avenues for medicinal innovation.

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SPECIALIZED PRO-RESOLVING LIPID MEDIATORS (SPMS): EMERGING CHEMICAL SIGNALS IN THE RESOLUTION OF INFLAMMATION

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Abstract:

Inflammation is a critical physiological response that facilitates host defense and tissue restoration following injury or infection. However, when this process fails to resolve appropriately, it can drive the development of chronic conditions such as rheumatoid arthritis, atherosclerosis, neurodegenerative diseases, and malignancies. Traditionally perceived as a self-limiting phase, the resolution of inflammation is now recognized as an active and highly orchestrated biological process. Central to this resolution are Specialized Pro-Resolving Lipid Mediators (SPMs), a distinct group of lipid-derived molecules — including lipoxins, resolvins, protectins, and maresins — synthesized from omega-3 and omega-6 polyunsaturated fatty acids. These mediators promote the clearance of apoptotic cells, suppress further neutrophil infiltration, and restore tissue equilibrium without inducing immunosuppression. In contrast to conventional anti-inflammatory therapies that broadly suppress immune activity, SPMs engage specific G-protein-coupled receptors to reprogram immune cell responses toward resolution. This chapter offers a detailed comparison between classical pro-inflammatory mediators and SPMs, emphasizing their biosynthesis, receptor signaling, cellular roles, and translational relevance in chronic inflammatory pathologies. It highlights a transformative shift in pharmacological strategies—focusing not on immunosuppression but on enhancing endogenous resolution mechanisms—ushering in a new era of targeted therapies for persistent inflammation.

Introduction:

Inflammation is a highly conserved, multifaceted biological process initiated in response to tissue injury, infection, or exposure to noxious agents. It is characterized by a series of cellular and molecular events involving vascular permeability, leukocyte recruitment, and the release of soluble inflammatory mediators. These events aim to eliminate the inciting insult, repair tissue damage, and restore homeostasis[1]. While acute inflammation is a protective response and typically resolves after the removal of the offending stimulus, its persistent or dysregulated activation can culminate in chronic inflammation, contributing to the pathogenesis of numerous non-communicable diseases, including rheumatoid arthritis, inflammatory bowel disease (IBD), atherosclerosis, neurodegenerative disorders, and certain malignancies[2,3].

Historically, the resolution of inflammation was considered a passive phenomenon, occurring after the cessation of pro-inflammatory signals. The decay of chemical mediators such as prostaglandins, leukotrienes, and cytokines was thought to be sufficient for inflammation to subside. However, emerging evidence over the past two decades has challenged this classical view, establishing that inflammation resolution is not passive but an active and coordinated process, tightly regulated by endogenous chemical signals[4,5].

A pivotal discovery in this paradigm shift is the identification of Specialized Pro-Resolving Lipid Mediators (SPMs) — a novel class of bioactive molecules that actively mediate the resolution phase of inflammation. These mediators include lipoxins, resolvins, protectins, and maresins, which are enzymatically synthesized from omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), particularly arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)[6,7].

SPMs exhibit potent pro-resolving and anti-inflammatory actions that extend beyond the suppression of cytokine production. They actively promote the clearance of apoptotic cells (efferocytosis), enhance tissue remodeling, inhibit further neutrophil infiltration, and restore tissue integrity without compromising host immune defense[8]. This is in stark contrast to conventional anti-inflammatory therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, which, while effective in dampening inflammation, often induce broad immunosuppression, predisposing patients to infection and delayed healing[9].

Moreover, SPMs exert their effects by binding to specific G-protein-coupled receptors (GPCRs) on immune and stromal cells, thereby initiating signal transduction pathways that reprogram cellular responses from pro-inflammatory to pro-resolving states[10]. The therapeutic potential of SPMs has gained significant attention in recent years due to their role in limiting chronic inflammation, promoting tissue repair, and resolving infections in models of inflammatory diseases.

This chapter provides a comprehensive overview of the role of chemical mediators in inflammation, contrasting classical pro-inflammatory mediators with the newly discovered specialized pro-resolving mediators. Emphasis is placed on the biosynthesis, receptor interactions, mechanisms of action, and clinical relevance of SPMs, particularly in the context of chronic inflammatory pathologies and the potential for next-generation therapeutic development.

Chemical Mediators of Inflammation

The acute inflammatory response is governed by an intricate interplay of chemical mediators that orchestrate vascular alterations, immune cell recruitment, and activation at the site of injury or infection. These mediators are secreted by various resident and infiltrating immune cells, including mast cells, macrophages, neutrophils, endothelial cells, and platelets. Their coordinated actions lead to increased vascular permeability, enhanced leukocyte adhesion, and

the activation of intracellular signaling pathways that culminate in pathogen elimination and tissue repair. However, the same mediators that are crucial for early defense may, when dysregulated, contribute to tissue injury, fibrosis, or the transition to chronic inflammation if not timely resolved or downregulated [11,12].

Among the early mediators released is histamine, a vasoactive amine predominantly secreted by mast cells during allergic responses and tissue damage. It acts primarily through H1 receptors on endothelial cells to induce vasodilation and increased vascular permeability, facilitating immune cell migration to inflamed tissues [13]. Prostaglandins, synthesized from arachidonic acid via the cyclooxygenase (COX) pathway, also play central roles. PGE_2 and PGI_2 contribute to vasodilation, pain perception, and fever, and PGE_2 in particular modulates the activity of T-helper 17 (Th17) cells, thereby linking innate and adaptive immune responses [14]. Leukotrienes, especially LTB_4, act as potent chemoattractants for neutrophils, while cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are implicated in bronchial constriction, vascular leakage, and mucus secretion, which are hallmark features in allergic and asthmatic responses [15].

Other important mediators include Platelet-Activating Factor (PAF), a phospholipid-derived molecule synthesized by activated platelets, neutrophils, and endothelial cells. PAF enhances leukocyte adhesion, platelet aggregation, and chemotaxis, while also promoting degranulation and the release of secondary inflammatory signals [16]. In parallel, cytokines such as TNF-α, IL-1β, and IL-6 are rapidly upregulated during inflammation, initiating acute-phase responses and inducing adhesion molecule expression on vascular endothelium, thereby promoting immune cell infiltration. Chemokines, such as CXCL8 (IL-8), create concentration gradients that direct neutrophils and other immune cells to the site of inflammation [17]. These cytokines act synergistically to amplify the inflammatory cascade and sustain leukocyte activation at the lesion site.

In addition, the production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), including nitric oxide (NO), further amplifies the inflammatory response. These molecules are generated by activated neutrophils and macrophages to eliminate invading pathogens through oxidative mechanisms. However, when produced in excess, ROS and RNS inflict collateral tissue damage, enhance endothelial dysfunction, and exacerbate inflammatory signaling through redox-sensitive transcription factors [18]. While all these mediators are indispensable for initiating host defense, their unregulated activity poses a risk for persistent inflammation and chronic tissue injury. Hence, effective resolution is essential—a process not governed by mere cessation of pro-inflammatory signals, but actively directed by a distinct class of endogenous mediators, particularly Specialized Pro-Resolving Lipid Mediators (SPMs), which reprogram immune responses to restore homeostasis [19].

Transition from Inflammation to Resolution

Historically, the resolution of inflammation was considered a passive phase that followed the neutralization or withdrawal of pro-inflammatory triggers. This view presumed that inflammatory responses naturally faded as cytokines, prostaglandins, and leukotrienes dissipated from the tissue microenvironment. However, recent discoveries in immunopharmacology have revealed that resolution is not a passive process but rather an active, genetically programmed, and highly orchestrated biological sequence. This phase is regulated by a class of endogenous lipid mediators known as Specialized Pro-Resolving Lipid Mediators (SPMs), which include lipoxins, resolvins, protectins, and maresins. Unlike classical mediators that promote leukocyte recruitment and cytokine release, SPMs limit further neutrophil infiltration, enhance macrophage-mediated efferocytosis, and initiate tissue repair, thus facilitating the return to homeostasis without causing systemic immunosuppression [20,21].

A key event enabling this transition is the lipid mediator class switch, a biochemical shift that transforms the inflammatory environment from one dominated by pro-inflammatory eicosanoids to one enriched with pro-resolving lipid mediators. During the early phase of inflammation, enzymes like cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) facilitate the production of prostaglandins and leukotrienes. As inflammation proceeds, changes in the local cytokine milieu and intercellular communication—particularly involving neutrophils, macrophages, and endothelial cells—promote the induction of enzymes like 15-lipoxygenase (15-LOX), which drive the biosynthesis of SPMs from omega-3 polyunsaturated fatty acids such as EPA and DHA. This temporal regulation of lipid mediator profiles is crucial for ending the inflammatory response and initiating resolution and repair mechanisms [22,23].

Specialized Pro-Resolving Lipid Mediators (SPMs)

Specialized Pro-Resolving Lipid Mediators (SPMs) represent a unique class of bioactive compounds that are enzymatically derived from essential polyunsaturated fatty acids (PUFAs), primarily omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These mediators are not merely anti-inflammatory but are actively involved in promoting resolution, enabling the return to tissue homeostasis without suppressing host defense. The major families of SPMs include lipoxins, resolvins, protectins, and maresins. Although each group follows a distinct biosynthetic pathway and interacts with specific receptors, they collectively function to suppress excessive leukocyte infiltration, enhance efferocytosis, and restore tissue architecture following injury [24].

- **Lipoxins** Lipoxins are the first identified family of pro-resolving lipid mediators and are synthesized from arachidonic acid (AA) via lipoxygenase (LOX)-mediated pathways, particularly involving 15-LOX and 5-LOX. This biosynthesis is often transcellular, requiring cooperative enzymatic interactions between cells such as neutrophils and

platelets. The two principal forms, Lipoxin A_4 (LXA_4) and Lipoxin B_4 (LXB_4), exert their biological effects through ALX/FPR2 receptors expressed on neutrophils and macrophages. Through these interactions, lipoxins inhibit neutrophil transmigration, enhance monocyte recruitment, and stimulate macrophage-mediated efferocytosis, thereby facilitating the clearance of apoptotic cells and resolution of inflammation [25].

- **Resolvins**

  Resolvins are sub-classified into E-series (derived from EPA) and D-series (derived from DHA) based on their parent fatty acid. RvE1 and RvE2 are major E-series resolvins, while D-series members include RvD1 through RvD6. These lipid mediators act on G-protein-coupled receptors (GPCRs) such as ChemR23 for RvE1 and GPR32/ALX for RvD1, modulating immune cell behavior at sites of inflammation. Resolvins function by reducing neutrophil infiltration, downregulating the production of pro-inflammatory cytokines, and enhancing macrophage phagocytosis of apoptotic cells. These actions are central to halting the inflammatory response and promoting tissue recovery [26,27].

- **Protectins** Protectins are also derived from DHA and are synthesized via 15-LOX-mediated oxygenation. The most studied molecule within this class is Protectin D1 (PD1), which is also referred to as Neuroprotectin D1 (NPD1) when found in neuronal tissues. PD1 has been shown to exert neuroprotective, anti-apoptotic, and anti-inflammatory effects. It reduces the migration of leukocytes, suppresses cytokine production, and preserves neuronal integrity under conditions of oxidative stress or neuroinflammation. These features make protectins of particular interest in the treatment of neurodegenerative diseases such as Alzheimer's disease [28].

- **Maresins**

  Maresins, short for macrophage mediators in resolving inflammation, are synthesized from DHA via the 12-LOX pathway, predominantly within macrophages. Maresin 1 (MaR1) is the most well-characterized member and is involved in promoting wound healing, tissue regeneration, and resolution of infections. Maresins inhibit neutrophil infiltration and enhance the phagocytic capacity of macrophages, facilitating efficient clearance of apoptotic debris. Notably, MaR1 has been shown to enhance tissue repair without impairing microbial clearance, making it a promising candidate for therapeutic development in chronic inflammatory and infectious diseases [29].

- **Biosynthesis Overview** The biosynthesis of SPMs occurs through transcellular mechanisms involving cooperative enzyme activity between different immune and structural cells. For example, neutrophils interacting with platelets contribute to lipoxin formation, while macrophages and endothelial cells participate in the generation of resolvins and maresins. The enzymes responsible for this biosynthetic switch include 5-

lipoxygenase (5-LOX), 15-lipoxygenase (15-LOX), and 12-lipoxygenase (12-LOX). Their spatial and temporal regulation dictates the transition from pro-inflammatory eicosanoids to pro-resolving mediators. This enzymatic reprogramming is essential for terminating inflammation and orchestrating resolution without compromising immune surveillance or tissue integrity [30].

Mechanism of Action of Specialized Pro-Resolving Lipid Mediators (SPMs)

Unlike traditional anti-inflammatory agents that broadly suppress immune function, SPMs play an active role in immune reprogramming to facilitate resolution of inflammation. They do not merely block inflammatory signals but orchestrate a return to tissue homeostasis through receptor-mediated signaling, efferocytosis, and regulation of immune cell function. These actions help eliminate cellular debris, attenuate neutrophil-driven tissue damage, and promote tissue repair — all while preserving the host's antimicrobial defense mechanisms. A defining feature of SPM action is their interaction with specific G protein-coupled receptors (GPCRs) expressed on various immune and epithelial cells [31,32].

Each subclass of SPMs interacts with distinct GPCRs to initiate specialized signaling cascades. Lipoxins, such as LXA_4, bind to ALX/FPR2 receptors found on neutrophils, monocytes, and macrophages, reducing neutrophil chemotaxis and enhancing efferocytosis [33]. Resolvin E1 (RvE1) interacts with ChemR23 (also known as ERV1) receptors on macrophages and dendritic cells, leading to suppression of cytokine production and promotion of tissue repair [34]. Resolvin D1 (RvD1) binds both GPR32 and ALX/FPR2, enhancing macrophage clearance of apoptotic cells and contributing to inflammation resolution [35]. Meanwhile, Protectin D1 (PD1/NPD1) and Maresin 1 (MaR1) signal through less fully characterized GPCRs but are known to promote cell survival, limit oxidative stress, and exert protective effects particularly in neuronal and epithelial tissues [36]. Activation of these receptors leads to the inhibition of NF-κB signaling, reduced expression of pro-inflammatory genes, suppression of neutrophil recruitment, and increased anti-inflammatory gene transcription.

At the cellular level, SPMs exert pleiotropic effects across different immune and structural cell types. In neutrophils, SPMs block transendothelial migration, reduce degranulation, and limit the production of reactive oxygen species, thereby preventing collateral tissue damage [37]. In macrophages, SPMs shift the phenotype toward a pro-resolving M2-like profile, characterized by enhanced efferocytosis, reduced pro-inflammatory cytokine release, and upregulation of tissue repair genes [38]. Endothelial cells also respond to SPMs by stabilizing vascular barrier function, reducing the expression of adhesion molecules such as ICAM-1 and VCAM-1, and preventing excessive leukocyte infiltration [39]. Furthermore, SPMs modulate the adaptive immune system by attenuating T cell proliferation and dendritic cell maturation, leading to reduced antigen presentation and limiting the perpetuation of chronic inflammatory responses

[40]. These multifaceted actions underscore the therapeutic promise of SPMs in managing chronic inflammatory diseases without the adverse effects associated with immunosuppressive therapies.

Clinical Relevance of SPMs in Chronic Diseases

herapeutic Applications of Specialized Pro-Resolving Lipid Mediators (SPMs) Specialized pro-resolving lipid mediators (SPMs) offer a novel therapeutic paradigm for addressing chronic inflammatory and immune-mediated diseases. Unlike conventional anti-inflammatory drugs that suppress immune activation, SPMs actively promote inflammation resolution, debris clearance, and tissue regeneration while preserving antimicrobial host defenses. In disorders such as rheumatoid arthritis (RA) and osteoarthritis (OA), agents like resolvin D1 (RvD1), maresin 1 (MaR1), and lipoxin A_4 (LXA_4) have demonstrated preclinical efficacy by reducing joint inflammation, modulating cytokines such as TNF-α and IL-1β, and limiting cartilage degradation [43]. Similarly, in respiratory conditions like asthma, SPMs reduce airway hyperresponsiveness, inhibit eosinophilic infiltration, and restore epithelial barrier function through leukotriene inhibition and cytokine suppression [44].

In the cardiovascular system, chronic inflammation underlies the progression of atherosclerosis, where SPMs contribute by enhancing plaque stability, reducing monocyte recruitment, and promoting clearance of apoptotic foam cells. Studies in $ApoE^{-/-}$ mice models show that RvD1 and MaR1 can attenuate vascular inflammation and stimulate lesion regression [45]. Within the central nervous system, SPMs like protectin D1 (PD1/NPD1) and MaR1 have been identified for their neuroprotective properties in models of Alzheimer's disease, where they limit microglial activation, inhibit β-amyloid accumulation, and support neuronal survival [46]. In inflammatory bowel disease (IBD), SPMs suppress neutrophil influx, reduce epithelial apoptosis, and promote mucosal healing, thereby restoring barrier integrity in models of ulcerative colitis and Crohn's disease [47].

Emerging data also support the potential of SPMs in oncology, where chronic inflammation can promote tumor progression and immune evasion. Interestingly, SPMs such as RvE1 have been shown to enhance dendritic cell function, improve antigen presentation, and stimulate anti-tumor T cell responses, suggesting a role in immune surveillance and resolution within the tumor microenvironment [48]. Collectively, these findings highlight the vast therapeutic potential of SPMs in treating a wide spectrum of diseases through immune reprogramming and resolution pharmacology. As research advances, the development of stable SPM analogs and delivery systems may pave the way for targeted, side-effect-free interventions in both inflammatory and immunopathological conditions [41,42].

Future Directions and Challenges

The discovery of Specialized Pro-Resolving Lipid Mediators (SPMs) has introduced a transformative perspective in inflammation research, moving beyond suppression to the promotion of active resolution. Despite their promising biological roles in restoring immune balance and tissue homeostasis, several scientific and translational hurdles must be overcome to fully harness their therapeutic potential. One of the foremost challenges lies in the short half-life and metabolic instability of native SPMs, which limits their bioavailability and clinical applicability. Developing synthetic analogs or delivery systems that preserve bioactivity while enhancing stability is a key area for future research.

Additionally, standardized analytical techniques for accurately quantifying SPMs in biological fluids and tissues remain underdeveloped. The lack of validated biomarkers hampers the ability to monitor resolution status or predict treatment efficacy in clinical settings. Moving forward, high-resolution lipidomics and targeted metabolomics may facilitate more precise profiling of SPM dynamics in health and disease. Moreover, our current understanding of SPM receptor signaling pathways is incomplete. Elucidating the full spectrum of receptor-ligand interactions, downstream signaling cascades, and their tissue-specific effects will be essential for targeted drug design.

From a therapeutic standpoint, clinical translation remains in its infancy. Although preclinical studies in models of arthritis, asthma, atherosclerosis, neurodegeneration, and colitis have shown encouraging outcomes, large-scale human trials are still needed to evaluate the safety, efficacy, and dosing strategies of SPM-based interventions. Regulatory and manufacturing challenges, particularly related to scalability, purity, and formulation, also pose significant barriers. Finally, integrating SPMs into precision medicine frameworks, where patient-specific inflammatory profiles guide therapeutic decisions, represents a promising yet complex frontier.

In conclusion, while SPMs represent a paradigm shift in the management of chronic inflammation, realizing their full clinical impact will require concerted efforts in drug development, biomarker discovery, systems biology, and personalized healthcare approaches. Addressing these challenges through interdisciplinary research will pave the way for resolution-focused therapies that are both effective and immunologically safe.

Conclusion:

The discovery of Specialized Pro-Resolving Lipid Mediators has significantly expanded our understanding of the inflammatory process — not merely as a destructive cascade, but as a biphasic, actively regulated event involving both initiation and resolution. SPMs — including lipoxins, resolvins, protectins, and maresins — represent a paradigm shift in inflammation pharmacology, focusing not on immunosuppression but on immune restoration and homeostasis.

By promoting efferocytosis, tissue repair, and resolution, SPMs offer a therapeutic advantage in a wide spectrum of chronic inflammatory and autoimmune disorders. Their ability to act without compromising host immunity sets them apart from conventional anti-inflammatory agents.

Although challenges such as metabolic stability, targeted delivery, and regulatory approval remain, the ongoing research into SPM analogs, novel formulations, and biomarker-based patient stratification holds promise. As our understanding deepens, SPMs may pave the way for a new generation of pro-resolving therapeutics, altering the trajectory of chronic inflammatory disease management.

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OPTIMIZATION OF PHASE SHIFT CONTROLLERS USING ADAPTIVE FUZZY LOGIC SYSTEM FOR A POWER ELECTRONICS HYBRID SYSTEM

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Abstract:

The increasing demand for electrical energy in the nations is satisfied by hybrid systems. The mismatching of hybrid systems leads to the phase shift in the three-phase signals, producing more harmonics in the band of 2 to 150kHz. However, due to various factors, harmonics have arisen from the Resonance based Impedance Type Hybrid Active Filter (RITHAPF) and Thyristor Controlled Reactor (TCR) which act as the phase shift controller in hybrid systems. Therefore, the Adaptive Fuzzy controller is employed with RITHAPF and TCR to maintain the phase shift and attenuate the harmonics produced, which outperforms the Hysteresis controller by 17.5% approx. in harmonic suppression and the simulation carried out for various phase angles.

Keywords: Hybrid Power Electronics Adaptive Fuzzy Controller, Harmonics suppression, RITHAPF, TCR, Supraharmonics, Hybrid Active Filter.

1. Introduction:

Hybrid systems have evolved to combat the augmenting needs of electrical energy. Combining the output of different energy sources makes an uninterrupted power supply possible. This reduces the uncertainty of the power systems. This method increases reliability, reduces the dependence on a single source, and increases the system's overall efficiency. The role of power electronics is to condition, convert, and control of input energy sources to different forms. In hybrid systems, the role of power electronics is quite difficult. The downside of the hybrid systems is initial cost for installation, modelling, and accumulation of energy from various sources is a difficult task and maintaining the system. The hybrid sources are connected hence it is the need to address the issues in all ranges of the system to design an efficient power grid system.

The system quality depends on the amount and quality of the power generated. On the otherhand, quality of the signals affects the system's reliability. The harmonics formed due to the mismatch in the system is the main reason for the deteriorating signals. The harmonics are the signal waveform of integral multiples of the original frequency of the fundamental waveform. In power electronics the harmonics are the root cause of mismatched non-linear loads, high-frequency operation of power electronics devices, magnetic saturation produced in transformers, inductive devices, resonance caused due to the interaction of capacitors and inductors in the transformers, capacitors banks, and transmission lines, fault situations like short circuit and asymmetrical conditions like unbalanced loads. The harmonics produced range of 2 to 150kHz is called supraharmonics formed in the power grid system due to varying amounts of power obtained from the sources. When the hybrid sources are connected, it is important to address the supraharmonic suppression.

In the paper [1], the authors inscribed the importance of supra harmonics suppression to increase the system's power quality, hence the authors proposed the Hybrid Power Filter (HPF) contains active and passive parts in it. The active section works as the linear power amplifier which suppresses the high frequency component harmonics and the passive section reduces the fundamental frequency component harmonics. A detailed review of harmonic sources is done in the paper [2] where the authors presented a detailed study of sources like electric vehicle sources, green energy generation sources, electric arc furnace loads, residential loads, and electric vehicular loads. The authors of this paper gave good guidance of the modern power systems and its negative impact overcoming too. The micro-grid systems contain the Voltage Source Converter (VSC), where the current and voltage harmonics takes place that results in the negative impact of the whole system performance is explained in the paper [3] by stochastic modelling. The paper [4] is presented by IEEE PES Renewable technologies to address the recent issues in the power electronics systems like configurations, unit measures, energy management and control, etc to maintain the power grid systems' energy sustainability. The Artificial Intelligence based Neural Network (ANN) and fuzzy based Adaptive Neuro Fuzzy Inference Systems (ANFIS) are proposed for two models of hybrid power grid systems like wind and solar renewable sources for simulation in the paper [5] and the 11^{th} and 13^{th} harmonic distortion is taken for simulation that shown ANFIS is efficient in both the hybrid system models.

In the papers [6], [8]-[11], Adaptive Fuzzy Controllers (AFC) is used for the harmonic suppression in the hybrid grid system. The power factor is obtained closely to one value and the Total Harmonic Distortion (THD) is controlled using the PSO-based adaptive fuzzy controller in the Hybrid Active Filter (HAPF). In the paper [8], an adaptive fuzzy hysteresis current-controlled active power filter in hybrid shunt configuration is proposed for power compensation

in reactive components and harmonic distortion range which uses the low-rated elements like active power filter and shunt passive filters. The paper [9] used Active Power Filter (APF) and Passive Power Filter (PPF) in series to the power grid system and uses the Adaptive Fuzzy controller using PI is proposed which attenuates by matching the magnitude of frequency of APF and PPF. The Multi-Objective Genetic Algorithm (MOGA) based AFC is proposed by the authors in the paper [10] for harmonics mitigation in Photovoltaic Renewable Energy Sources (RES) using APF. The effects of torque ripple, eddy current loss, and average torque were also demonstrated. DC De-icing model with an active filter and an AFLC is proposed for four substations of 220KV is presented in the paper [11] which attenuates the harmonics efficiently.

The paper [7] discusses the topics on the kinds of harmonic and inter-harmonic for different frequency groupings of the power systems and comparison using Total Harmonic Distortion (THD) parameter is used for assessing the power inverters is made. The fuzzy based optimisation is chosen in the papers [12], [17-20], [24] using active filter, passive filters and optimization technique to reduce the harmonics of the power grid systems. The reason for harmonics in the converter and inverters are mainly due to the small signal stability issues is addressed in the paper [13]. This paper derives the systematic transfer function for harmonics in small signal analysis for linear models ac-dc converters. The nonlinear loads and Hybrid Passive Filter (HPF) are used to mitigate the harmonics present in voltage and current of the power system. Constrained Optimization is used for tunning the parameters of HPF is done to attenuate the harmonics. The harmonics produced due to unreasonable resonance occurred in the passive filter and line inductances are addressed in the paper [15] which is combated using the variable conductance tunning-based hybrid filters which employs the 7^{th} order tuned passive filter and active filter in serial connection with source. The adaptive hysteresis current control and Synchronous Reference Frame is used for the reference signal generation of controller for current signals is proposed in the paper [16] along with the hybrid active power filters which reduces the THD range of the system effectively.

From the review it is identified that harmonic distortion deteriotes the quality of the signals. In the hybrid systems due to mismatch of the signals more harmonic distortions are present. This paper concentrates on the supraharmonics which is present due to the backslide of the Resonance based Impedance Type Hybrid Active Filter (RITHAPF) and Thyristor Controlled Reactor (TCR) of the hybrid system which is overcome using the Adaptive Fuzzy Controller (AFC).

2. Analysis of Total Harmonic Distortion (THD)

The harmonics in general is the waved whose frequency is the integral multiple of the fundamental frequency of the reference signal. The harmonics are usually unintentionally produced waveforms from the converter and inverter of the power electronic systems. In order to

attenuate this unwanted signal, a clear calculation of number of harmonics present in the system is required which is defined by the term THD. The THD is mathematically defined by ratio of sum of Root Mean Square (RMS) of all the harmonics present in the system to the fundamental RMS of the signal which is given in the (1),

$$THD = \frac{\sqrt{V_2+V_3+\cdots\ldots+V_N}}{V_1} \quad (1)$$

where V_1 is the fundamental frequency

V_2, V_3, ….V_n are the harmonics frequencies.

3. Hybrid Power Electronics Systems

A Power Electronics Hybrid System (PEHS) consisting of two or more input Renewable Energy Sources (RES) may be wind turbines, solar, geothermal, tidal energy etc. The block diagram of PEHS shown in Figure 1. Hybrid systems are employed to overcome the dependency on a single source and to meet the needs of electrical energy due to more applications and a growing population. The energy from the RES system is given as input to rectifiers which convert ac to dc signals. Then the signals are sent to the filter which may be active or passive that is depends on the application and design. The converter in the block diagram helps to increase the gain of the input signal using the high-gain converters. Then the energy is stored in the storage device for the future use. The stored energy is supplied to different kinds of loads according to the application. Figure 2 represents the configuration diagram of the hybrid model.

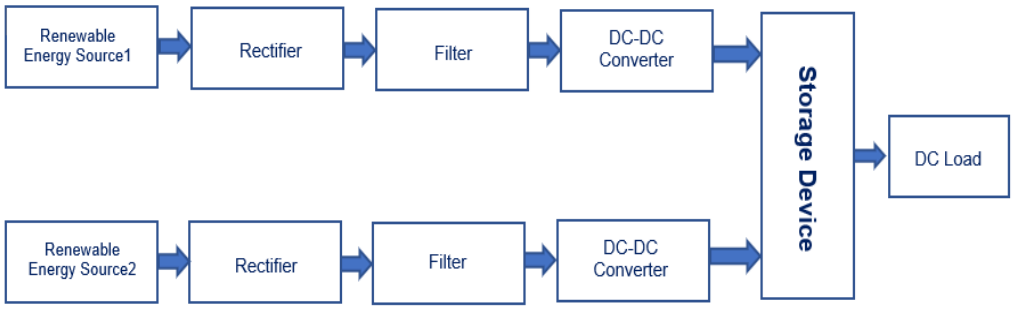


Fig. 1: Power Electronics Hybrid System Block Diagram

The Thyristor Controlled Reactor (TCR) [22] is the device used in the power electronics for controlling the phase of the signals according to the varying load conditions. It is made of reactance which effectively varies from zero to desired value according to the loads with the help of thyristor valve. The firing angle theoretically between 90° to 180° but in practical little deviations are present. The major disadvantage of the TCR is it cannot promptly switch between ON and OFF conditions this leads to the generation of harmonics. This is mainly due to reactive component present in the circuit. The instantaneous TCR current equation is given in the (2),

$$i(t) = \frac{v_{rms}}{2\pi fl}(cos\alpha - cos180) \quad (2)$$

On the other hand, the Resonance based Impedance Type Hybrid Active Filter (RITHAPF) [21]is of active elements and passive elements for filtering purposes. The reactive components present in this filter leads to the phase shift of the fundamental signal which gets added or subtracted with the fundamental signals leads to the generation of harmonic waves. The RITHAPF has good advantage for matching the loads but its main drawback is the phase shift happening in the filtered signal.

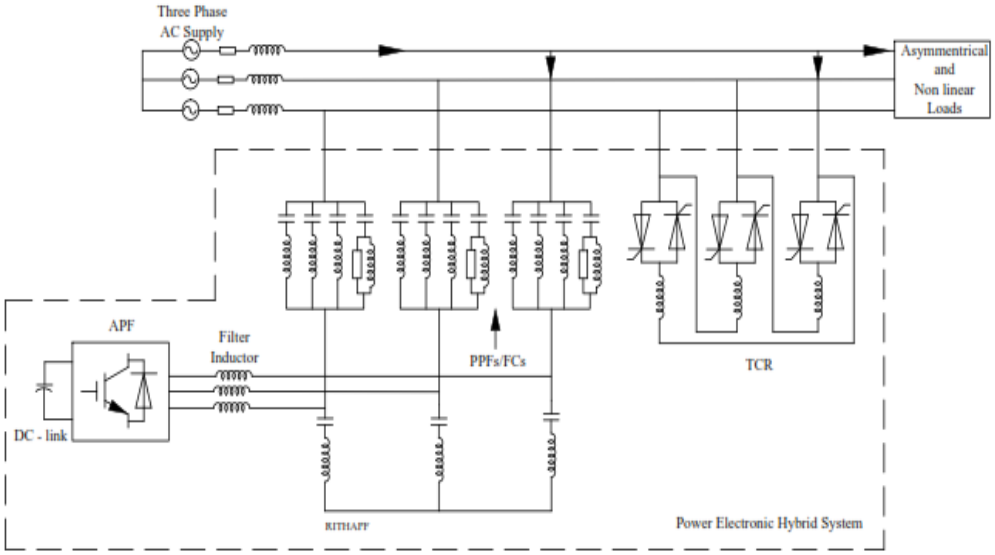


Fig. 2: Simulink diagram of PEHS

4. Proposed Model

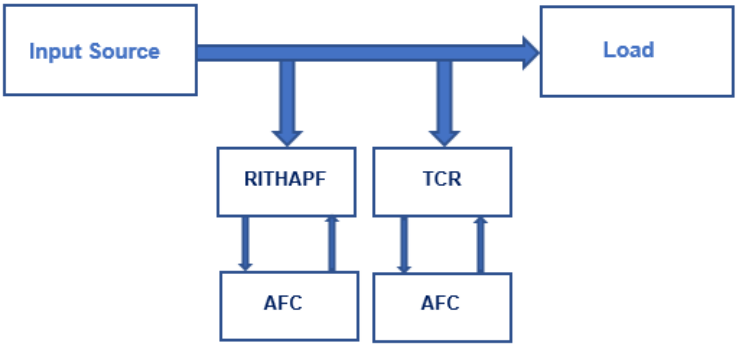


Fig. 3: Proposed System Model

Adaptive Fuzzy Controller (AFC) is the enhanced version of the fuzzification and defuzzification process which functions in a compatible manner to the system. Its main principle is adjusting the parameters according to the needs of the system. The three steps of AFC [23] is collecting the data samples, adjusting of controller parameters and enhancing the controller efficiency. The Figure 3 represents the proposed model where the AFC is used in RITHAPF and TCR to reduce the harmonics.

RITHAPF Harmonic Suppression

Let us consider the input signals be x_1, x_2 …..x_n and the phases of the signals are represented by α_1, α_2….. α_N. Using the Adaptive Fuzzy Controller, the error in the phase of the signal with the fundamental frequency is calculated using the equation (3),

$$e(t) = \alpha_1(t) - \alpha_n(t) \quad (3)$$

where $\alpha_n(t)$ is the n^{th} harmonics of the input signal.

From the value of error, e(t), the adjusting parameter 'k' is derived by the Adaptive Fuzzy Controller depends on the phase shift taken in the input signal with respect to the fundamental frequency. The 'K' parameters consist of K_1,K_2,…..K_n values based on the fuzzification required for every input signal. The output of the AFC is given by the equation,

$$\gamma(t) = x_1(t) + \mu(t) \quad (4)$$

Where K= k_1, k_2,…..k_n are adjusting parameters of Adaptive Fuzzy Controller and the function of μ(t) is given by,

$$\mu(t) = k_1\alpha_2 + k_2\alpha_3 + \cdots + k_n\alpha_{n+1} \quad (5)$$

The formula for generalized phase value is given by,

$$\alpha = tan^{-1}\left(\frac{X_L - X_C}{R}\right) \quad (6)$$

Where the X_L and X_C are the reactance and R is the resistance of the Filter.

The Adaptive Fuzzy Logic Control is given by,

$$K = \theta(e(t)) \quad (7)$$

Thus by obtaining the 'K' adjusting parameter values after fuzzification the output of the fuzzy controller produces the signals in the fundamental frequency which reduces the formation of harmonic signals in the RITHAPF filter of the Hybrid Active Filter.

TCR Harmonic Suppression

In the Thyristor Controlled Reactor, the Adaptive Fuzzy Controller shifts the phase of the signals either in the 90° or 180° to maintain the phase variation in order to reduce the harmonics. The Adaptive Fuzzy Controller function for TCR is given by,

$$K = \varphi(f(t)) \quad (8)$$

Where f(t) is the error function obtained from the signal.

$$f(t) = \cos\ (360^{\circ} \_ \emptyset) \quad (9)$$

The output of Adaptive Fuzzy Controller for TCR is given by,

$$\gamma(t) = x_1(t) + \beta(t) \quad (10)$$

Where the β(t) is the adjusted signals obtained by fuzzification.

$$\beta(t) = x_2 cos\gamma_2(t) + x_3 cos\gamma_3(t) + \cdots + x_n cos\gamma_n(t) \quad (11)$$

Therefore, the fuzzification and the defuzzification is carried out sum of all the signals which results in high voltage gain without the harmonics.

5. Implications

The proposed work is processed using the MATLAB and SIMULINK software using the simulation parameters discussed in the table 1. In the Figure 4 the simulation is carried out for AFC and hysteresis controller for Power Electronics Hybrid Systems. The Hysteresis controller is conventional method for reducing the harmonics of the system by increasing the voltage in the hysteresis band. The input source voltage of 400V with the fundamental frequency 50Hz is given as input to the PEHS. The TCR of 5H is used and the inductor and capacitor of 2mH and 20µF is used in RIPTHAF filter.

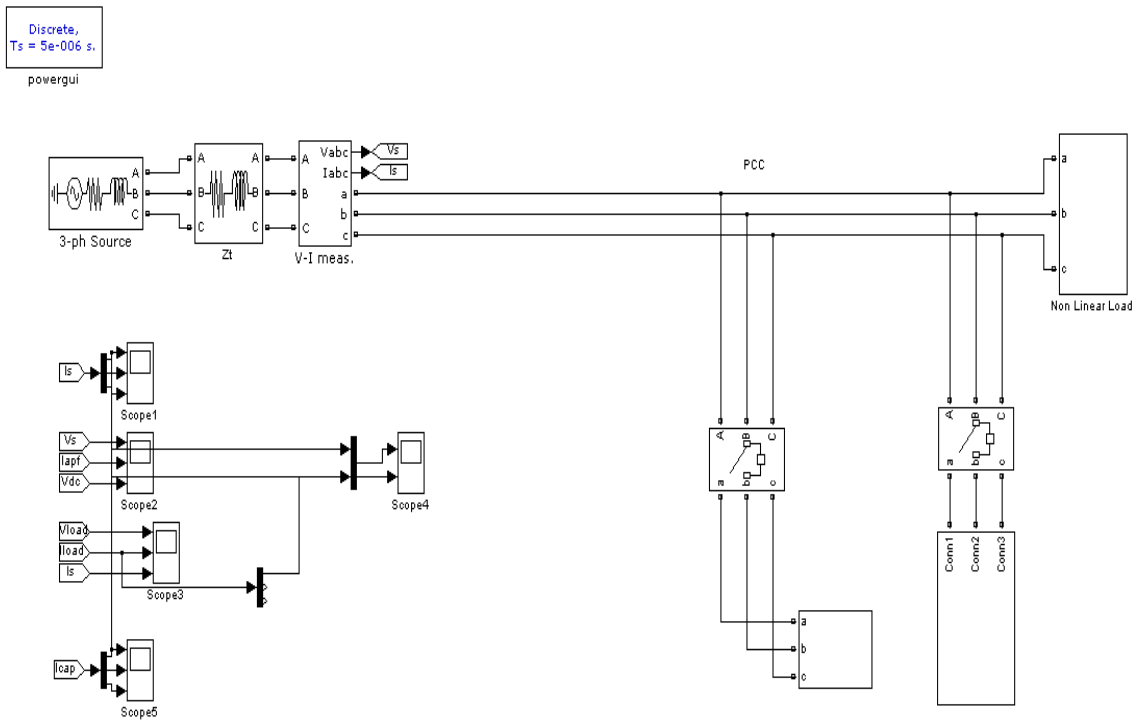
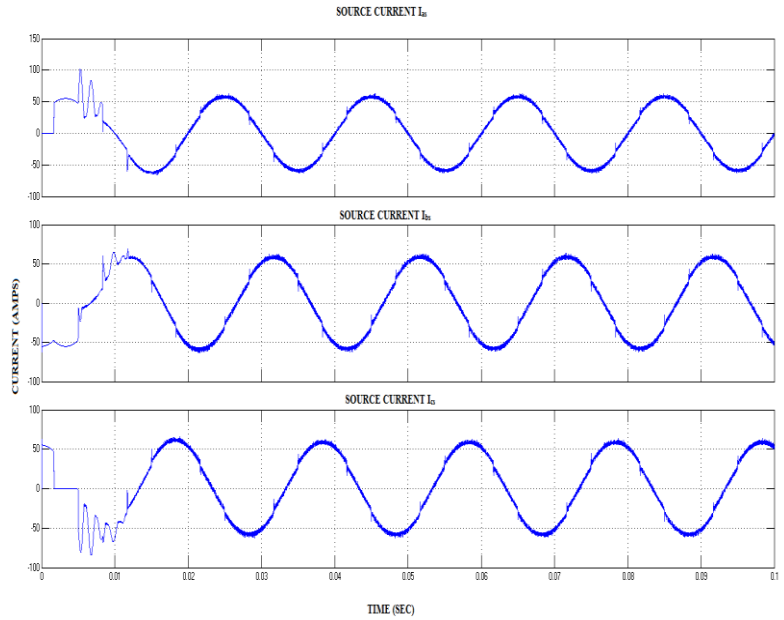


Fig. 4: SIMULINK Model of AFC and Hysteresis Controller based PEHS

Table 1: Simulation Parameters

Variables	Values
Fundamental Frequency (f)	50Hz
Impedance	0.01+0.000001Ω
Inductor	2mH
Capacitor	20µF
TCR	5H
Line voltage	400V
Load	1000 Ω



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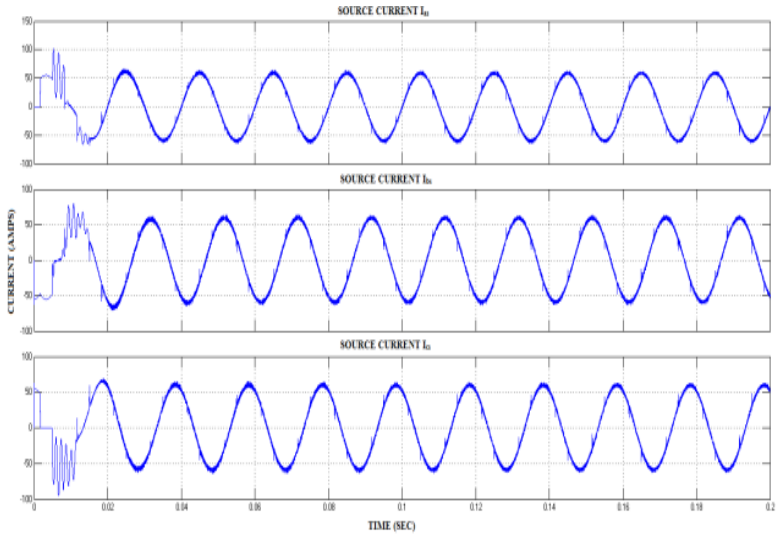


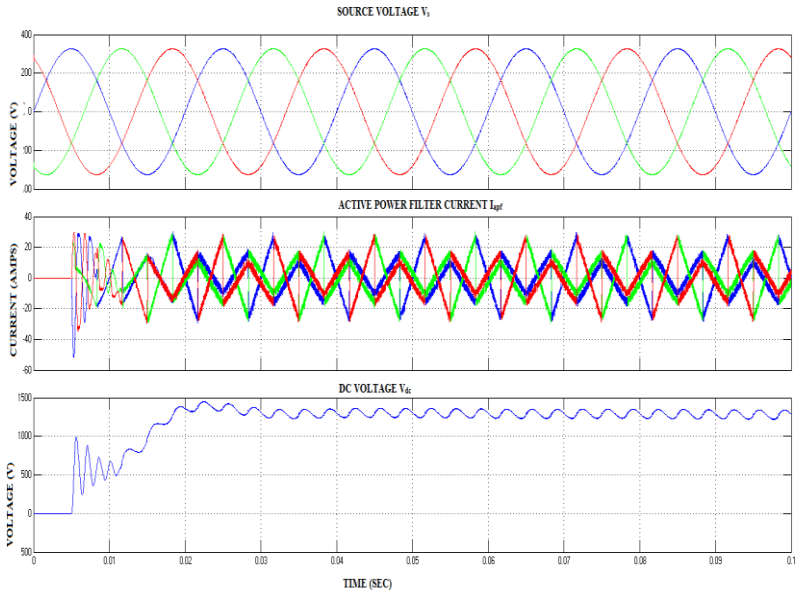
b)

Fig. 5: Input waveform of a) Hysteresis Controller and b) Adaptive Fuzzy Controller

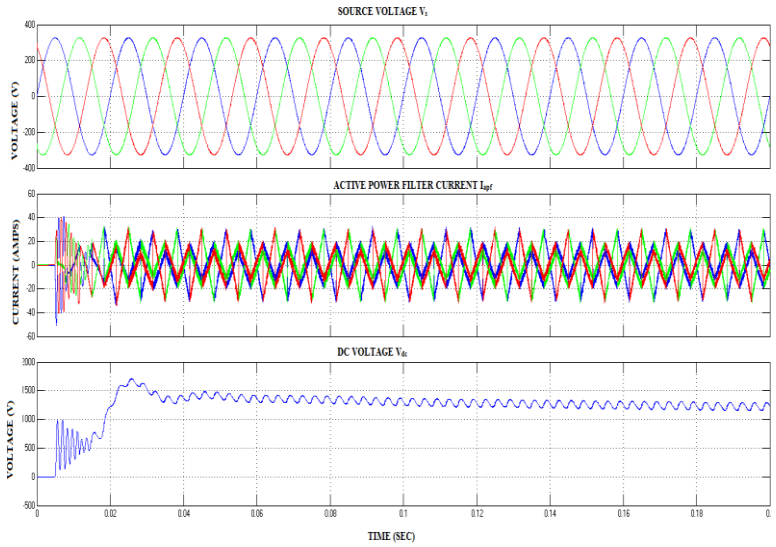
The Figure 5 shows the input waveform of three phase line system of the hybrid system using the Hysteresis and Adaptive Fuzzy Controller. From the waveform of both controllers, it is seen that the harmonics present in the input waveform reduced in the proposed work where their smooth waveform is obtained without harmonics. This is done with the help of maintaining the constant phase shift among the three phase signals which results in the harmonic attenuations both by RITHAPF and TCR in the PEHS using AFC.

Figure 6 depicts the waveforms of source voltage, Active Power Filter current and dc voltage of the hysteresis controller and Adaptive Fuzzy Controller. In the AFC voltage source waveform, the phase shift is maintained at regular intervals with the smooth waveform and the current waveform of filter has less harmonics compared to the hysteresis controller. On

visualising the dc voltage waveforms, the AFC based PEHS attains constant output at less time compared to the hysteresis controller.



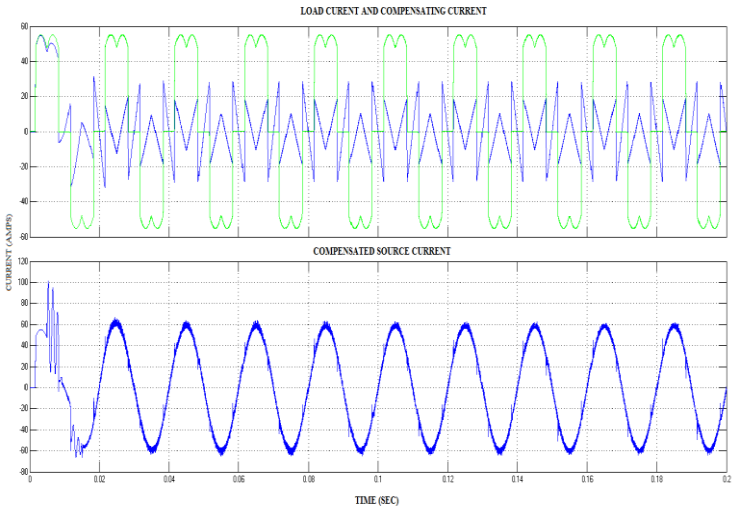
a)



b)

Fig. 6: Representation of V_s, I_{APF} and V_{dc} of a) Hysteresis Controller b) Adaptive Fuzzy Controller

Figure 7 is the output load current and compensation current waveform of the hysteresis controller and AFC. The hysteresis controller load output is not constant with more harmonics compared to the AFC.



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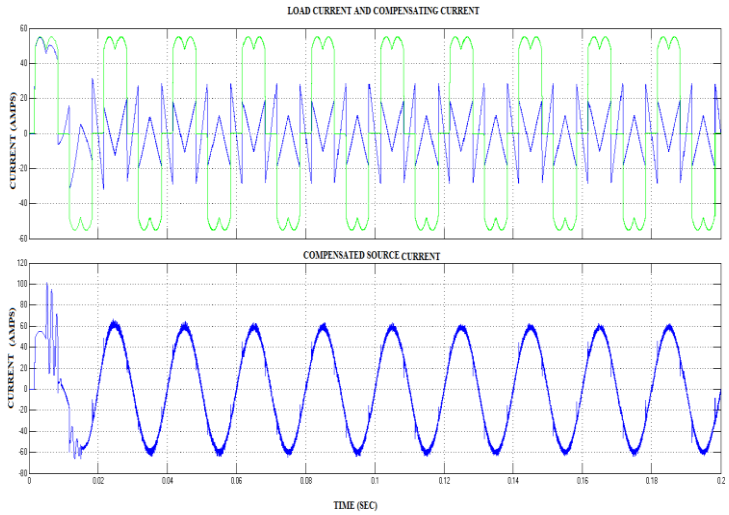
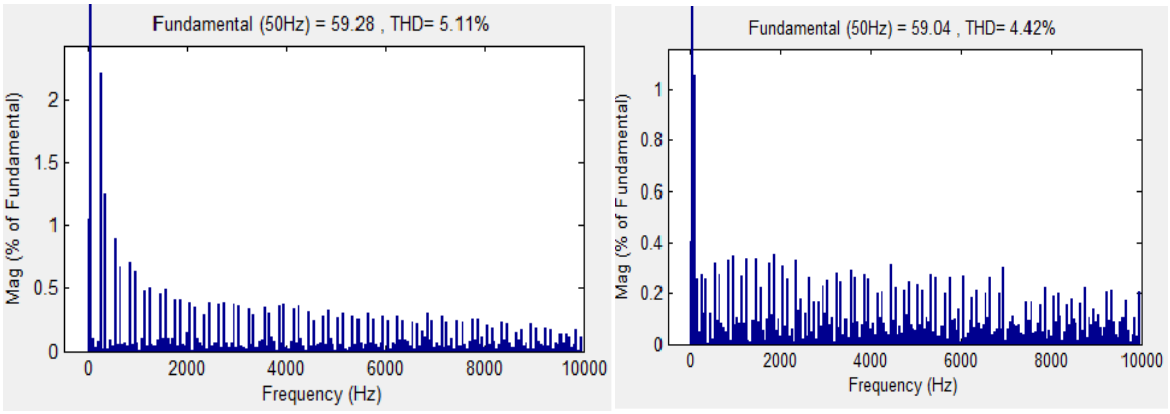


b)

Fig. 7: Representation of I_L and I_{comp} of a) Hysteresis Controller b) Adaptive Fuzzy Controller

The Figure 8 is the representation of frequency domain analysis of hysteresis and AFC controller using Fast Fourier Transform analysis where the AFC shown 4.42% reduction in harmonics compared to Hysteresis controller by maintaining the appropriate phase of the signals irrespective of the operation it is carried out.

The Table 2 is the simulation obtained from by changing the phase degree [25] of the input waveforms to study the proposed model resilience towards practical scenario. It is seen that for all the phase shift of 0°, 90° and 180°, there is the little variations in the output and maintains the THD suppression at approximately same range. The difference in the THD of Hysteresis controller and the AFC also shown constant output of 17.5% approximately.



a) Hysteresis Controller **b) Adaptive Fuzzy Controller**

Fig. 8: Frequency Domain Analysi

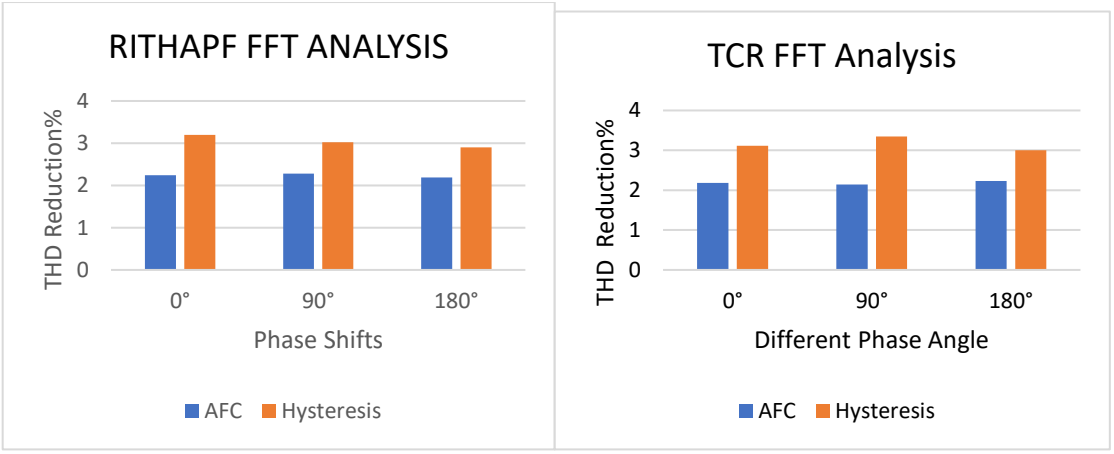


Fig. 9: THD Percentage Reduction in RITHAPF and TCR

Table 2: Simulation Results for Three Different Phase shifts

S. No	Phase Variations	Variables	THD	
			Hysteresis	AFC
1	0°	V_s	5. 09%	4.50%
		I_s	0.23%	0.20%
		I_{APF}	30%	30.27%
		I_{comp}	4.90%	4.02%
2	90°	V_s	5.13%	5.02%
		I_s	0.19%	0.17%
		I_{APF}	29.96%	29.75%
		I_{comp}	5.10%	4.80%
3	180°	V_s	4.90%	4.02%
		I_s	0.23%	0.19%
		I_{APF}	31.15%	30.65%
		I_{comp}	5.51%	4.92%

Figure 9 represent the percentage variation in THD separately at TCR and RITHAPF using Hysteresis controller and the proposed AFC Controller obtained from the Fourier Frequency domain analysis at different phase shifts.

Conclusions:

The proposed work of employing Adaptive Fuzzy Controller in the RITHAPF and TCR is done to reduce the supraharmonic present in the system due to the mismatch of elemets or loads present in the system. The mathematical analysis for the proposed work is presented. The SIMULINK is used to represent the proposed work where the outputs are provided in the implication part. From the outputs obtained it is seen that the Adaptive Fuzzy Controller outperforms the Hysteresis Controller which are depicted in the sourece voltage, load current, filter current, compensation current output waveforms. The phase shist is maintained appropraite in three phase of the signals so that the harmonics are reduced in the frequency range of 2 to 150kHZ. The FFT analysis also done which shown 17.41% higher efficiency in the harmonic attenuation compared to the Hysteresis controller.

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MICROALGAL BIOACTIVES: POTENTIAL AND PROSPECTS IN BIOTECHNOLOGY

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Abstract:

Microalgae are emerging as a sustainable and versatile platform for the production of bioactive compounds with wide-ranging applications in the food, pharmaceutical, cosmetic, and aquaculture industries. These unicellular photosynthetic organisms are rich sources of high-value metabolites such as carotenoids, phycobiliproteins, polyunsaturated fatty acids (PUFAs), phenolic compounds, polysaccharides, sterols, vitamins, and minerals. These compounds exhibit potent antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory properties, making them ideal candidates for nutraceutical and therapeutic development. Among the various microalgal genera, Dunaliella species are recognized for their capacity to accumulate carotenoids, especially β-carotene, lutein, and zeaxanthin. In the highlighted study, a novel halotolerant strain Dunaliella sp. ZP-1 was isolated and characterized for its high biomass yield. Through ethyl methanesulfonate (EMS) mutagenesis, a mutant strain "tyd4" was developed, exhibiting significantly enhanced lutein and zeaxanthin production. Additional improvements in biomass were achieved through red light cultivation and exogenous melatonin application. This advancement demonstrates the potential of strain improvement and stress modulation in elevating the commercial viability of microalgae for natural carotenoid production. This seminar aims to explore the diversity, function, and application of microalgal bioactive compounds, with emphasis on recent biotechnological advancements that enhance metabolite yield.

Keywords: Micro Algae, Antioxidant, Carotenoids, Bioactive Compounds**.**

Introduction:

- **Microalgae** are a diverse (include cyanobacteria and eukaryotic organisms) of microscopic autotrophic organisms with the size ranging from a few micrometers to hundreds of micrometers (Pereira *et al.,* 2020).
- Capable of photosynthesis, found in freshwater and marine environments, and considered a promising source of biomass and bioactive compounds (Balasubramaniam *et al.,* 2021)
- Humans used microalgae for the first time 2000 years ago, when the Chinese used Nostoc to withstand a famine (Choopani *et al.,* 2016).

Classification

Cyanophyta (cyanobacteria)
Chlorophyta (green algae)
Bacillariophyta (diatoms)
Haptophyta
Rhodophyta (red algae
Euglenophyta
Chryosphyta (golden algae)

Why Microalgae

Microalgae are gaining attention for their vast potential in various fields due to several remarkable advantages. They are a rich source of bioactive metabolites and demonstrate broad-spectrum biological activities, making them valuable in pharmaceuticals, nutraceuticals, and cosmetics. Their eco-friendly and sustainable mode of production contributes to environmental conservation, while their renewable nature ensures long-term viability. Microalgae can be scaled up easily for diverse applications and offer significant potential in wastewater treatment due to their ability to absorb pollutants. Furthermore, they exhibit a high exponential growth rate, enabling rapid biomass production and making them highly efficient for industrial and environmental use.

What are Bioactive Compounds

Bioactive compounds are a diverse group with a diverse chemical assembly (hydrophilic or lipophilic), that produce a biological effect in living tissues or organisms. These effects may be positive or negative, depending on the compound's nature, dose, and bioavailability (Guaadaoui *et al.,* 2021). Bioactive compounds possess antioxidant activity, enzyme inhibition activity, can inhibit receptor activities, and can also inhibit gene expression.

Bioactive Compounds from Microalgae

Microalgae are a rich source of diverse bioactive compounds with significant nutritional and therapeutic value. These include pigments such as carotenoids, chlorophylls, and phycobiliproteins, which possess strong antioxidant properties. They are also known for producing polyunsaturated fatty acids like EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid), and GLA (gamma-linolenic acid), which are beneficial for heart and brain health. Polysaccharides from microalgae, including sulfated polysaccharides and exopolysaccharides, offer antimicrobial and immunomodulatory properties. In addition, microalgae contain phenolic compounds such as polyphenols and flavonoids, which are powerful antioxidants. They also synthesize phytosterols, including ergosterols and cholesterol derivatives, known for their cholesterol-lowering effects. Lastly, microalgae are an excellent source of vitamins and minerals,

notably vitamin B12, vitamin E, and essential minerals like iron (Fe), magnesium (Mg), and zinc (Zn), making them a valuable supplement for human health and nutrition.

1. Carotenoids

Carotenoids are a class of lipid-soluble pigments synthesized by microalgae, plants, and some bacteria. Carotenoids in microalgae function not only as accessory pigments in photosynthesis—playing a crucial role in light harvesting—but also as potent antioxidants that protect cells from oxidative stress caused by high light intensity and reactive oxygen species. The carotenoids also have the property of activating the transcription factor, Nrf2 (nuclear factor erythroid-2-related factor-2), which adds into triggering the antioxidant gene expression in particular cells and tissues (Sachindra *et al.,* 2007).

Carotenoids are divided into:

- Carotenes (e.g., β-carotene)
- Xanthophylls (e.g., astaxanthin, lutein, zeaxanthin)

Carotenoid	**Microlagal Source**
B-carotene	*Dunaliella salina*
Astaxanthin	*Haematococcus pluvialis*
Lutein	*Chlorella zofingiensis*
Zeaxanthin	*Spirulina platensis*
Canthaxanthin	*Chlorella vulgaris*

2. Chlorophyll

- Chlorophyll is a green, magnesium–porphyrin pigment essential for photosynthesis in microalgae, higher plants, and cyanobacteria. It captures light energy, primarily in the blue and red wavelengths, and converts it into chemical energy, serving as a vital biomolecule in primary producers.
- t is used as a natural food coloring agent and has antioxidant as well as antimutagenic properties.
- It has a long hydrophobic phytol tail, helping it anchors to thylakoid membranes in chloroplasts.
- Chlorophyll and its derivative chlorophyllin exhibit strong bioactivity by neutralizing reactive oxygen species (ROS), binding to mutagens like heterocyclic amines and aflatoxins to prevent DNA damage, and reducing the expression of pro-inflammatory cytokines to combat inflammation. (Begum *et al.,* 2016)

3. Phycobiliproteins

- Phycobiliproteins are brightly colored, water-soluble pigment–protein complexes found in cyanobacteria, red algae, and some cryptophytes.

- Acting as photosynthetic antenna pigments, absorb light in the green to orange range wavelengths that chlorophyll cannot and transfer this energy to chlorophyll a in the photosystem II, thereby enhancing light harvesting in low-light environments.
- Pigments like phycocyanin suppress the production of inflammatory cytokines (e.g., TNF-α, IL-6). These pigments neutralize ROS and free radicals by donating electrons through their conjugated double bonds and metal-binding properties, preventing oxidative damage.

Phycobiliproteins	Color	Source	Approx yield (% dry weight)
Phycoerythrin	Red-pink	*Porphyridium, Gracilaria*	10-15%
Phycocyanin	Blue	*Spirulina platensis*	5-8%

4. Poly Unsaturated Fatty Acids

- Polyunsaturated fatty acids (PUFAs) are fatty acids with two or more double bonds in their carbon chain, essential for maintaining cell membrane integrity and involved in inflammation regulation, cardiovascular health, and brain development.
- Microalgae serve as the primary producers of long-chain PUFAs (LC-PUFAs), including omega-3 and omega-6 fatty acids, which are transferred to fish through the food web and contribute significantly to the nutritional quality of aquatic organisms(Tomdio, Ritchie, & Miller, 2019)
- Oscillatoria spp. are one among the many cyanobacteria capable of producing fatty acids.
- PUFAs downregulate the enzyme **HMG-CoA reductase**, the key enzyme in making cholesterol in the liver.

PUFA	Source	PUFA content (% dry wt)
EPA (Eicosapentaenoic Acid) C20:5 (n-3)Omega-3	*Nannochloropsis sp., Phaeodactylum tricornutum*	30-50 % of total lipid
DHA (Docosahexaenoic Acid) C22:6 (n-3)Omega-3	*Crypthecodinium cohnii, 134chizochytriums p.*	20-50% of total lipid
ALA (Alpha-linolenic Acid) C18:3 (n-3)Omega-3	*Precursor of EPA and DHA, Chlorella sp., Scenedesmus sp.*	40-50% of total lipid
ARA (Arachidonic Acid) C20:4 (n-6)Omega-6	*Porphyridium cruentum, Parietochloris incisa*	10-15% of total lipid
GLA (Gamma-linolenic Acid) C18:3 (n-6)Omega-6	*Spirulina platensis*	20-14% of total lipid

5. Polysaccharides

- Polysaccharides are long-chain carbohydrates composed of repeating monosaccharide units linked by glycosidic bonds.
- In microalgae, they occur as intracellular storage forms like starch or as extracellular structural forms such as sulfated polysaccharides and mucilage.
- Sulfated polysaccharides exhibit particularly antiviral activity by blocking virus attachment and entry into host cells, through their negatively charged sulfate groups and structural mimic of host cell receptors. (Ibrahim *et al.,* 2023).

Polysaccharide	Structure	Source Microalgae
Sulfated galactans	Sulfated polymers of galactose	*Porphyridium cruentum*
Xylans and mannans	Hemicellulose-type polysaccharides	*Chlorella vulgaris*
β-1,3-glucans	Branched glucose polymers	*Euglena gracilis*
Uronic acid-rich EPS	Contains uronic acids	*Cyanobacteria, Microcystis*
Arabinoxylans	Arabinose and xylose units	*Spirulina platensis*

6. Phenolic compounds

- Phenolic compounds are low molecular antioxidant secondary metabolites characterized by one or more hydroxyl groups attached to aromatic rings.
- In microalgae, they play a role in defense and stress response mechanisms .
- Phenolic compounds enhance cellular antioxidant capacity by upregulating enzymes involved in oxygen metabolism and xenobiotic detoxification, while simultaneously downregulating signaling pathways associated with inflammation.
- Some polyphenols fight ssRNA-positive viruses by blocking the spread of reactive oxygen species inside cells. (Li *et al.,* 2007)

Phenolic compounds	Types
Simple phenols	Catechol, hydroxybenzoic acid
Flavonoids	Quercetin, luteolin
Phenolic acids	Gallic acid, caffeic acid, ferulic acid

7. PhytoSterols

- Phytosterols are lipophilic triterpenes with a hydroxyl group, structurally similar to cholesterol, and are important components of cell membranes.
- In microalgae, they function as membrane stabilizers, it reduces cholesterol absorption, suppress inflammation, neutralize oxidative stress, and inhibit cancer cell growth by mimicking cholesterol and interfering with harmful cellular processes.

Sterol	Source	Function
Ergosterol	*Chlorella, Scenedesmus*	Precursor of Vitamin D2, antifungal
Stigmasterol	*Chlorella vulgaris*	Anti-inflammatory, cholesterol-lowering
Brassicasterol	*Isochrysis galbana, diatoms*	Marine indicator, antioxidant
Fucosterol	*Navicula, Phaeodactylum*	Antidiabetic, anti-obesity

Applications

1. Nutraceuticals

- A number of microalgae have been classified as Generally Regarded as Safe (GRAS) and approved by the US Food and Drug Administration (FDA).
- According to Watanabe 2019, microalgae species of cyanobacteria e.g., Spirulina, Aphanizomenon and Nostoc are hugely harvested for the food industry.

2. Pharmaceuticals

Microalgae-derived compounds hold significant promise in the pharmaceutical field due to their diverse bioactivities. For instance, C-phycocyanin, a pigment from microalgae, has demonstrated strong anticancer potential by inhibiting the growth of various cancer cell lines, including liver cancer (HepG2), human leukemia (K562), and lung cancers (A549 and NSCLC),

as reported by Martinez Andrade et al. (2018). Additionally, sulfated exopolysaccharide from *Porphyridium cruentum* has shown antiviral effects by effectively inhibiting the cytopathic activity of viruses such as HSV-1, HSV-2, and VZV, with CP_{50} values ranging from 0.7 to 5 μg/mL. In terms of cardioprotective effects, a carotene mixture derived from *Dunaliella salina*, consisting of approximately 60% cis-isomers and 40% trans-isomers, was found to be more effective in reducing lipid, cholesterol, and triglyceride levels than synthetic all-trans-β-carotene. Lastly, microalgae also show antibacterial properties; for example, noscomin has exhibited activity against harmful bacteria including *Bacillus cereus*, *Staphylococcus epidermidis*, and *Escherichia coli* (Jaki *et al.,* 1999).

3. Cosmetics

Microalgae have shown immense potential in the cosmetic industry due to their anti-ageing, sun protection, and skin-whitening properties. For anti-ageing, compounds like lutein**,** derived from *Scenedesmus salina*, are known for their ability to protect the skin from UV radiation. Similarly, lycopene, a carotenoid, is commonly used in skincare products to neutralize oxygen-derived free radicals, contributing to its anti-ageing effects (Pangestuti *et al.,* 2020). In terms of sun protection, violaxanthin, an orange-pigmented compound, effectively blocks harmful UVB radiation, decreases reactive oxygen species (ROS) production, and improves cell viability. Additionally**,** fucoxanthin has been shown to offer protective effects against sunburn. For skin whitening, the effect is primarily achieved by inhibiting tyrosinase, a key enzyme in melanin production. Pigments such as zeaxanthin and astaxanthin exhibit strong anti-tyrosinase activity, making them valuable ingredients in cosmetic products aimed at skin lightening. A 2017 study also highlighted the potential of a novel, non-fastidious freshwater microalga (*Chlorella emersonii* KJ725233) for use in cosmeceuticals, owing to its anti-ageing, antioxidant, and anti-inflammatory properties.

4. Aquaculture

- Microalgae have been used in aquaculture to feed fish and other economically important creatures like molluscs and crustaceans.
- The preferred protein ingredient of feed in aquaculture is still fishmeal, but nowadays microalgae are used worldwide as an alternative protein-rich source.
- In fish feeding trials, many types of microalgae biomass have been found to be useful for increasing fish growth and to improve the bioavailability, physiological activity, stress response, starvation tolerance, disease resistance and carcass quality (Sen Roy and Pal, 2015).
- Beside the protein content, the flesh pigmentation of fish is increased by carotenoids (beta-carotene with provitamin A activity, astaxanthin, lutein), chlorophylls, phycocyanin being essential for improving the taste and antioxidant capacity of the fish flesh.

- The commonly used microalgae in aquaculture are *Chlorella sp., Tetraselmis sp., Isochrysis sp., Pavlova sp., Phaeodactylum sp., Chaetoceros sp., Nannochloropsis sp., Skeletonema sp.* and *Thalassiosira sp.* (Priyadarshani and Rath, 2012)

Summary:

Microalgae are a promising source of bioactive compounds with significant applications in various fields. These compounds include pigments, polyunsaturated fatty acids, polysaccharides, phenolics, phytosterols, and essential vitamins and minerals. They exhibit a wide range of biological activities such as antioxidant, anti-inflammatory, anticancer, antiviral, and antibacterial effects. Due to their high growth rate, renewable nature, and ability to be cultivated sustainably, microalgae are increasingly used in pharmaceuticals, cosmetics, nutraceuticals, and environmental applications like wastewater treatment. Their versatility and functional potential make microalgae a valuable resource for health and industrial innovations.

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GOVERNING CONTINUOUS CANCER MONITORING: REGULATION, ETHICS AND PRIVACY

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Abstract:

Wearable and implantable cancer monitoring devices represent a transformative convergence of biomedical engineering, materials science, and digital health. These technologies enable continuous, real-time assessment of physiological parameters and molecular biomarkers, offering unprecedented opportunities for early detection, treatment optimization, and long-term surveillance of cancer patients. Wearable platforms ranging from epidermal patches and smart textiles to wristbands embedded with electrochemical sensors capture external signals such as sweat metabolites, skin temperature, and electrophysiological data. Implantable systems, including microelectrode arrays, biosensing implants, and smart stents, provide direct access to tumor microenvironments, measuring indicators like local pH, oxygenation, and tumor-associated antigens. Both classes of devices rely on advanced materials for flexibility, biocompatibility, and miniaturization, as well as on wireless power transfer and telemetry for continuous operation without frequent surgical interventions or cumbersome external hardware. Data collected are processed via edge computing and cloud platforms, incorporating machine learning algorithms to distinguish pathological patterns from physiological noise and to generate actionable insights for clinicians. Regulatory frameworks, ethical considerations, and patient privacy concerns present critical challenges that must be addressed to ensure safe and responsible deployment. Looking forward, integration with personalized medicine, adaptive smart materials, and telehealth ecosystems will further enhance the precision and accessibility of cancer care. This chapter provides a comprehensive overview of the design principles, current implementations, clinical applications, and future directions of wearable and implantable cancer monitoring devices.

Keywords: Wearable Sensors, Implantable Biosensors, Cancer Monitoring, Wireless Telemetry, Machine Learning

1. Introduction:

Cancer remains a leading cause of morbidity and mortality worldwide. Despite advances in imaging and molecular diagnostics, many cancers are detected at advanced stages, limiting treatment efficacy and survival rates. Traditional monitoring paradigms periodic blood tests,

imaging scans, or invasive biopsies provide only snapshots of tumor dynamics, often failing to capture rapid changes in the tumor microenvironment or systemic responses to therapy. Continuous, minimally invasive monitoring has emerged as a promising strategy to bridge this gap, offering real-time insights into disease progression and treatment response.

Wearable and implantable devices leverage recent innovations in microfabrication, flexible electronics, and biosensor technologies to gather rich, longitudinal data streams directly from patients. Wearables are typically non-invasive or minimally invasive devices worn on the skin or integrated into clothing, capable of measuring external proxies of disease activity, such as sweat biomarkers, skin temperature gradients, or electrocardiographic signals. Implantables, by contrast, are surgically or percutaneously introduced into the body either in peritumoral regions or systemic circulation to record biochemical and biophysical signals at their source, including local tissue oxygenation, interstitial fluid composition, and tumor-specific antigen levels [1].

Both platforms share key enabling components: (1) sensitive biorecognition elements (enzymes, antibodies, aptamers) for selective biomarker detection; (2) flexible, stretchable substrates and encapsulation materials to conform to dynamic tissue environments; (3) low-power electronics for signal conditioning, processing, and wireless communication; and (4) energy solutions such as wireless power transfer, energy harvesting, or microbatteries to sustain prolonged operation. Coupled with advances in machine learning and data analytics, these devices can transform raw biosignals into actionable clinical metrics, enabling early warning of relapse, adaptive therapy adjustments, and personalized risk assessments.

This chapter examines the state of the art in wearable and implantable cancer monitoring devices. Section 2 explores wearable sensor modalities, materials, and system architectures. Section 3 reviews implantable technologies, focusing on microscale biosensors, biocompatibility, and telemetry strategies. Section 4 addresses data transmission, edge/cloud processing, and analytical frameworks. Section 5 highlights clinical applications and illustrative case studies. Section 6 discusses regulatory pathways, ethical considerations, and data privacy challenges. Section 7 outlines emerging trends and future perspectives, including integration with personalized medicine and smart materials. The chapter concludes with a synthesis of opportunities and challenges on the horizon.

2. Wearable Sensors for Cancer Monitoring

2.1 Biosensor Modalities and Biomarker Targets

Wearable devices for cancer monitoring exploit a variety of sensing mechanisms electrochemical, optical, and electrophysiological to detect surrogate biomarkers in accessible biofluids or tissue interfaces. Sweat, interstitial fluid (ISF), and volatile organic compounds (VOCs) are primary targets. Electrochemical sensors functionalized with antibodies or aptamers can measure tumor-associated antigens (e.g., carcinoembryonic antigen, CEA) in sweat or ISF,

while optical sensors utilizing surface-enhanced Raman spectroscopy (SERS) can identify VOC signatures linked to metabolic alterations in cancer cells. Electrophysiological measurements, such as skin impedance or local electrical conductivity, have also been correlated with tissue perfusion changes around tumors, offering indirect but continuous readouts of angiogenesis and inflammatory processes.

2.2 Flexible Electronics and Materials

To maintain intimate contact with dynamic tissues, wearable cancer sensors rely on soft, conformable substrates such as polydimethylsiloxane (PDMS), polyurethane, and novel elastomeric composites. Conductive inks silver nanowires, graphene, or carbon nanotube networks are patterned into serpentine traces to withstand mechanical strains up to 50% without losing conductivity. Encapsulation layers protect the electronics from moisture and biofouling while permitting analyte diffusion. Recent advances in bio-inspired adhesives, including gecko-mimetic microstructures and bio-adhesive hydrogels, enable secure attachment to irregular skin surfaces without causing irritation [2].

2.3 Power Management and Energy Harvesting

Sustained operation of wearables requires efficient power solutions. Conventional micro batteries can add bulk and rigidity, so many systems incorporate energy harvesting modules piezoelectric generators that convert body motion or arterial pulses into electrical energy, thermoelectric generators exploiting skin-ambient temperature gradients, or photovoltaic cells integrated into textiles for light harvesting. Ultra-low-power system-on-chip (SoC) designs and duty-cycling strategies minimize average power consumption, enabling continuous monitoring for days or weeks on a single charge or harvested energy budget. Wireless charging via near-field communication (NFC) coils further simplifies maintenance by allowing non-contact recharging through clothing [3].

3. Implantable Devices for In Vivo Monitoring

3.1 Microscale Biosensing Platforms

Implantable devices offer the advantage of direct tumor microenvironment interrogation. Microelectrode arrays (MEAs) coated with enzyme layers (e.g., glucose oxidase for lactate sensing) or functionalized with antibodies can detect local concentrations of metabolites and tumor markers with high sensitivity. Ultrathin, injectable probes fabricated via atomic layer deposition and lithography minimize insertion trauma. Emerging wireless microsensors, measuring pH shifts or oxygen partial pressure, provide insight into tumor hypoxia, which correlates strongly with aggressiveness and therapy resistance [4].

3.2 Biocompatibility and Encapsulation

Long-term implantation demands rigorous biocompatibility to prevent foreign-body reactions. Hydrophilic hydrogel coatings reduce fibrotic encapsulation, while zwitterionic

polymers resist protein adsorption. Silk-derived biomaterials and biodegradable polymers (e.g., poly(lactic-co-glycolic acid), PLGA) can be engineered to degrade safely over defined timeframes, enabling transient diagnostics without explantation. Strategies to mitigate inflammatory responses include localized drug-eluting coatings that release anti-inflammatory agents (e.g., dexamethasone) in the immediate post-implantation phase.

3.3 Wireless Powering and Telemetry

Implantables eliminate external leads through wireless power transfer and telemetry. Inductive coupling at MHz frequencies can deliver milliwatts of power across a few centimeters, sufficient for sensing and wireless communication. Ultrasound-mediated power transfer achieves deeper penetration with minimal heating. Data uplink protocols leverage Bluetooth Low Energy (BLE), medical implant communication service (MICS) bands, or custom ultra-wideband (UWB) links to transmit sensor readings to external hubs. Miniaturized SoCs integrate power management, analogue front-ends, and digital processing, reducing implant size to sub-centimetres footprints [5].

4. Data Transmission, Processing, and Analytics

4.1 Wireless Communication Protocols

Robust data transmission from wearables and implantable relies on standardized wireless protocols. BLE is ubiquitous in consumer devices, offering low energy consumption and broad interoperability, while MICS bands (402–405 MHz) are licensed specifically for medical implants, providing reliable links in challenging tissue environments. Emerging protocols like IEEE 802.15.6 (body area networks) optimize for ultra-low power and coexistence with other wireless systems.

4.2 Edge Computing and Cloud Integration

To reduce latency and bandwidth demands, preprocessing algorithms noise filtering, feature extraction, and anomaly detection are executed at the edge (on-device or smartphone gateway). Key metrics (e.g., sudden spikes in biomarker levels) trigger event-driven uploads to cloud platforms for deeper analysis and long-term storage. Cloud infrastructures support data fusion from multiple sensors and users, enabling population-level analytics and development of predictive models [6].

4.3 Machine Learning for Signal Interpretation

Interpreting biosensor data requires distinguishing true pathological signals from artifacts (motion, temperature fluctuations, biofouling). Supervised machine learning classifiers (random forests, support vector machines) and deep neural networks excel at pattern recognition in high-dimensional feature spaces. Transfer learning approaches allow models trained on one patient cohort to adapt to new individuals with minimal retraining. Crucially, explainable AI techniques

(e.g., SHAP values) enhance clinical trust by identifying which features drive algorithmic predictions [7].

5. Clinical Applications and Case Studies

5.1 Early Detection and Screening

Pilot studies have demonstrated wearable patches capable of detecting exhaled breath VOCs associated with lung and breast cancers, achieving sensitivity and specificity comparable to low-dose CT scans in small cohorts. Implantable lactate sensors in peritumoral regions have signaled early metabolic shifts preceding radiographic tumor progression by up to two weeks, enabling pre-emptive therapy adjustments.

5.2 Real-Time Therapy Monitoring

In chemotherapy and immunotherapy, continuous monitoring of biomarkers such as circulating tumor DNA (ctDNA) fragments via subcutaneous interstitial fluid sensors has provided real-time feedback on treatment efficacy. Sudden drops in ctDNA levels correlate with tumor regression, while rebounds signal emerging resistance, guiding oncologists in modifying dosage or switching regimens without waiting for scheduled imaging [8].

5.3 Prognostic and Predictive Uses

Longitudinal sensor data have been integrated with clinical variables to develop prognostic indices that outperform static staging systems. For instance, combining trends in skin temperature asymmetry (from wearables) with local pH measurements (from implants) yields composite scores predictive of wound healing complications in post-surgical cancer patients, supporting personalized rehabilitation plans [9].

6. Regulatory, Ethical, and Privacy Considerations

6.1 Regulatory Pathways and Approval

Wearable and implantable cancer monitoring devices occupy a unique regulatory niche, often blurring the traditional boundaries between consumer electronics and medical hardware. In many jurisdictions, including the United States, devices intended to guide clinical decision-making or deliver therapeutic interventions must satisfy stringent medical-device regulations. The U.S. Food and Drug Administration (FDA) has recognized the potential of continuous-monitoring technologies through its Breakthrough Devices Program, which can accelerate the review timeline for innovations that offer significant advantages over existing standards of care. To qualify, developers must demonstrate plausible clinical benefit and a favorable risk-benefit profile for example, a wearable patch capable of detecting minimal residual disease earlier than standard imaging might gain priority review under this pathway [10].

Manufacturers must also adhere to established quality-management and safety standards. ISO 13485 provides a framework for quality-system requirements throughout the product lifecycle, from design and development to production, distribution, and post-market surveillance.

Electrical and electromagnetic safety must comply with IEC 60601 series standards, ensuring that device operation does not introduce unacceptable risks of shock, fire, or interference with other equipment. Implantable devices face additional hurdles: the FDA's premarket approval (PMA) route requires comprehensive biocompatibility testing under ISO 10993 protocols, demonstrating that materials will not provoke toxic or immunogenic reactions over the intended implantation period. Long-term stability studies are also mandated, verifying that sensors and electronics maintain accuracy and functionality in vivo over months or years. Moreover, developers must often conduct human factors engineering assessments to confirm that intended users whether patients, caregivers, or clinicians can operate devices safely and interpret readings correctly [11].

6.2 Patient Privacy and Data Security

Continuous physiologic monitoring inevitably generates large volumes of highly sensitive health data, raising critical concerns around confidentiality, integrity, and patient autonomy. To mitigate these risks, device ecosystems must implement robust, end-to-end encryption protocols both at rest on the device or gateway and in transit to cloud servers or clinician dashboards. Secure key management and routine vulnerability assessments are essential to defend against unauthorized access or data breaches. Regulatory frameworks such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in the European Union set baseline requirements for data handling, consent management, breach notification, and cross-border data transfer.

Beyond regulatory compliance, developers should adopt a data-minimization approach: transmitting only the processed or aggregated metrics necessary for clinical interpretation rather than raw high-frequency signals. This strategy not only reduces bandwidth and storage demands but also limits the potential exposure of granular patient data. Anonymization and pseudonymization techniques can further de-identify data for research or model-training purposes, ensuring that secondary uses remain within the scope of informed consent. Rigorous audit trails and role-based access controls help maintain traceability of who accessed or modified patient records, supporting both patient trust and regulatory inspections [12].

6.3 Ethical Implications of Continuous Monitoring

Persistent surveillance of physiologic and molecular signals introduces profound ethical considerations, particularly regarding patient autonomy, psychological well-being, and equitable access. Continuous monitoring can empower patients by providing actionable insights and enabling timely interventions; however, it may also foster anxiety, hypervigilance, or "data fatigue" if not managed sensitively. Informed consent processes must therefore be iterative and transparent, clearly delineating what parameters will be monitored, how alerts will be triaged,

who will have data access, and what steps follow an aberrant reading. Patients should retain the ability to pause monitoring or limit data sharing without jeopardizing their standard of care.

Algorithmic bias poses another ethical hazard. Machine-learning models trained on datasets lacking representation from diverse demographic or socioeconomic groups may underperform or generate misleading alerts in underserved populations. Developers must prioritize inclusive data collection and conduct bias-auditing to identify and correct disparities in model performance. Equitable access is also paramount: without thoughtful deployment strategies, continuous-monitoring technologies risk exacerbating health inequities by privileging patients in high-resource settings or those with digital literacy and connectivity. Integration with existing care pathways, insurance coverage models, and telehealth infrastructure should aim to democratize access, ensuring that the benefits of wearable and implantable cancer monitoring accrue broadly rather than to a select few.

Altogether, navigating the regulatory, privacy, and ethical landscape demands proactive planning, interdisciplinary collaboration, and an unwavering commitment to patient-centered design. By embedding these considerations early in development, innovators can deliver safe, effective, and socially responsible monitoring technologies that transform oncology care [13].

7. Future Perspectives and Emerging Trends

7.1 Integration with Personalized Medicine

The convergence of continuous biosensing with multilayered molecular profiling heralds a new era of precision oncology. In the coming decade, wearable and implantable devices will not operate in isolation but rather as integral components of a patient's digital health ecosystem, seamlessly interfacing with genomic, transcriptomic, and proteomic data. Imagine a scenario in which a patient's tumor biopsy yields a genomic "roadmap" of driver mutations and expression signatures; this map is then coupled in real time with dynamic measurements of circulating tumor DNA (ctDNA), metabolic by-products in interstitial fluid, and local tissue oxygenation. Advanced analytics platforms will integrate these disparate data streams, flagging early signs of therapeutic resistance or subclinical relapse long before conventional imaging or serum markers can detect changes.

Closed-loop therapeutic systems akin to the artificial pancreas in diabetes management will leverage continuous biomarker feedback to titrate drug dosing automatically. For example, an implantable sensor might monitor intertumoral pH shifts or lactate spikes that presage tumor proliferation; upon detecting a threshold breach, the system could trigger a micro-pump to release a calibrated dose of chemotherapy or immunomodulator directly into the tumor bed. Such "smart infusion" devices would minimize systemic toxicity by confining drug exposure to active disease sites, while adaptive algorithms learn each patient's unique response kinetics, refining dosing regimens over time [14].

Beyond pharmacologic control, these integrated platforms will support phenotypic stratification of patients in real time. Subgroups defined by on-demand sensor signatures such as rapid ctDNA clearance or inflammatory cytokine surges could be matched to tailored combination therapies, enrolling only those most likely to benefit. This model of n-of-1 trials, underpinned by continuous monitoring, stands to accelerate drug development and regulatory approval by demonstrating efficacy signals in highly personalized cohorts.

7.2 Smart Materials and Adaptive Systems

Central to next-generation biosensors are materials that respond dynamically to local biochemical and physical cues. Shape-memory polymers, for instance, can alter their conformation or porosity in response to temperature or pH, modulating analyte access to sensing elements. In a tumor microenvironment, where pH may dip below physiological norms, a hydrophobic membrane might transition to a hydrophilic state, permitting enhanced diffusion of acidic metabolites to an underlying electrochemical sensor. Once the local pH normalizes, the membrane reverts, preventing sensor saturation or fouling.

Stimuli-responsive hydrogels represent another frontier. Engineered to swell or contract in reaction to specific molecular triggers such as elevated glucose, lactate, or reactive oxygen species these networks can act as both recognition and amplification modules. By coupling hydrogel volume changes to optical or capacitive readouts, sensors can achieve ultrasensitive detection thresholds, discriminating minute biomarker fluctuations against background noise.

Self-healing conductive inks and stretchable electronics will address the durability challenges of long-term implantation. Microcracks induced by cyclic strain can be autonomously sealed through embedded microcapsules that release polymerization agents upon damage. Meanwhile, biodegradable electronic components fabricated from materials like magnesium or silk fibroin will enable transient implants that harmlessly resorb after completing their monitoring mission, eliminating the need for surgical retrieval and reducing chronic foreign-body reactions [15].

7.3 Convergence with Telehealth and AI

The rapid expansion of telemedicine infrastructure creates a natural home for wearable and implantable cancer monitors. Data streamed from patient devices can feed into cloud-based dashboards accessible by multidisciplinary care teams. Nurses and oncologists, empowered by real-time visualizations and predictive alerts, can conduct virtual clinic visits informed by objective biomarker trends rather than relying solely on patient self-reports.

Artificial intelligence will play a dual role in this ecosystem: first, at the edge, where compact neural networks embedded in the sensing device perform initial signal denoising and anomaly detection; and second, in the cloud, where federated learning approaches aggregate anonymized data across patient populations to refine predictive models without compromising

privacy. AI-driven virtual assistants may triage alerts differentiating benign fluctuations from clinically actionable events and coordinate next-step interventions, such as scheduling lab work, adjusting supportive medications, or prompting teleconsultations.

In survivorship care, continuous monitoring and remote support will mitigate the physical and psychological burdens of post-treatment surveillance. Automated check-ins via chatbots can remind patients to sync their devices, report symptoms, or complete patient-reported outcome measures. Should sensor data indicate early signs of recurrence such as rising ctDNA fragments an AI assistant could alert both patient and provider, triggering expedited diagnostic workups.

Together, these advances promise to redefine the patient journey in oncology from episodic, hospital-centric care to continuous, home-centered management. By embedding smart materials, closed-loop therapeutics, and AI-driven telehealth into a unified framework, the future of cancer care will be more proactive, personalized, and accessible than ever before [16].

Conclusion:

Wearable and implantable cancer monitoring devices stand at the forefront of a shift toward proactive, data-driven oncology. By providing continuous, high-resolution insights into tumor biology and patient physiology, these technologies have the potential to transform early detection, personalize therapeutic regimens, and improve long-term outcomes. Realizing this promise will require continued innovation in materials, microsystems, and analytics, coupled with robust regulatory frameworks and ethical governance. As these devices become increasingly integrated into clinical workflows and patient lifestyles, they will pave the way for a new paradigm in cancer care one that is predictive, preventive, and precisely tailored to each individual's unique disease trajectory.

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