Advanced Review and Research in Pharmaceutical Science

Editors

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Preface

The field of pharmaceutical science is undergoing a profound transformation driven by rapid advancements in technology, interdisciplinary integration, and an increasing emphasis on sustainability and patient-centric healthcare. The edited volume "Advanced Review and Research in Pharmaceutical Science" has been carefully compiled to present a comprehensive overview of recent developments, emerging trends, and innovative research shaping the future of pharmaceutical sciences.

This book brings together contributions from researchers, academicians, and industry experts, offering valuable insights into both fundamental and applied aspects of the discipline. The chapters included in this volume reflect the dynamic and evolving nature of pharmaceutical research, covering a wide spectrum of topics that are critical to modern healthcare and drug development.

The opening chapter on Advanced Analytical Techniques in Pharmaceutical Analysis highlights cutting-edge methodologies that enhance accuracy, sensitivity, and efficiency in drug analysis and quality control. This is followed by Advances in Experimental and Clinical Pharmacology, which explores recent progress in drug action, safety evaluation, and translational research bridging laboratory findings with clinical applications.

A significant focus of this book is sustainability and innovation in pharmaceutical manufacturing. The chapter on Zero-Waste Manufacturing of Oral Solid Dosage Forms presents eco-friendly approaches and green technologies aimed at reducing environmental impact while maintaining product quality. Complementing this, Quality by Design (QbD) and Quality Risk Management emphasizes systematic, science-based strategies to ensure consistent product performance and regulatory compliance.

The integration of technology with healthcare is another key theme addressed in Healthcare Monitoring Systems Using MANET, which discusses the role of mobile ad hoc networks in real-time patient monitoring and remote

healthcare delivery. Furthermore, Emerging Non-Pharmaceutical and Nanotechnology-Based Drug Delivery Approaches provides insights into novel delivery systems that improve drug targeting, bioavailability, and therapeutic efficacy.

Biotechnological advancements are also well represented, particularly in the chapter on Recombinant Therapeutics and Biotechnology in Diabetes Treatment, which explores innovative approaches to managing one of the most prevalent chronic diseases worldwide. Additionally, the inclusion of Environmental and Energy Applications reflects the expanding role of pharmaceutical sciences in addressing global challenges beyond healthcare.

This book aims to serve as a valuable resource for students, researchers, academicians, and professionals in pharmaceutical sciences and related fields. It not only provides a critical review of current knowledge but also encourages further research and innovation to meet future challenges in drug development, healthcare delivery, and sustainable practices.

We extend our sincere gratitude to all the contributing authors for their scholarly efforts and to the reviewers for their constructive feedback. We also acknowledge the support of the publishers in bringing this work to fruition.

It is our hope that this volume will inspire readers, foster scientific curiosity, and contribute meaningfully to the advancement of pharmaceutical science.

Editors

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Advanced Analytical Techniques in Pharmaceutical Analysis

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Abstract

Pharmaceutical analysis plays an essential role in drug discovery, development, manufacturing, and quality control. With the increasing complexity of modern therapeutics including biologics, nanoparticles, and complex small molecules advanced analytical techniques are indispensable for ensuring safety, efficacy, and regulatory compliance. This chapter presents an overview of state-of-the-art analytical methods used in pharmaceutical analysis, encompassing spectroscopic, chromatographic, mass spectrometric, and hyphenated techniques. Emphasis is placed on principle, instrumentation, applications, advantages, and limitations of each technique. Emerging trends such as high-resolution mass spectrometry, chemometrics, and real-time process analytical technology (PAT) are also discussed. The chapter concludes with a perspective on future challenges and developments.

Keyword: Pharmaceutical analysis, chromatography, mass spectrometry, spectroscopy, chemometrics, process analytical technology (PAT), hyphenated techniques

Introduction

Pharmaceutical analysis is defined as the qualitative and quantitative determination of drug substances and their formulation components. It is a cornerstone of pharmaceutical sciences, supporting all phases from preclinical research to post-marketing surveillance. Traditional analytical methods have been augmented by powerful modern tools capable of resolving complex mixtures with high sensitivity and selectivity. With advancements in regulatory expectations (e.g., ICH

guidelines), there is a growing need for robust analytical systems capable of detecting impurities, characterizing degradation products, and validating manufacturing processes. This chapter explores advanced analytical techniques that address these evolving needs.

Chromatographic Techniques

1. High-Performance Liquid Chromatography (HPLC)

HPLC remains one of the most widely used separation methods in pharmaceutical analysis. It offers high resolution, reproducibility, and adaptability. Recent innovations include ultra-high performance liquid chromatography (UHPLC), which employs sub-2 μm particles to achieve faster separations with improved efficiency.

Key Applications

- Quantification of active pharmaceutical ingredients (APIs)
- Impurity profiling
- Stability studies

2. Gas Chromatography (GC)

GC is suited for volatile and thermally stable compounds. Modern GC systems coupled with detectors like flame ionization detector (FID) and mass spectrometry (MS) allow for sensitive analysis of residual solvents, Flavors agents, and degradation products.

Spectroscopic Techniques

1. Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR provides detailed structural information without destroying the sample. It is particularly useful for elucidating drug structures, stereochemistry, and conformational analysis.

Advantages

- Non-destructive
- Quantitative capability without standards

Limitations

- Lower sensitivity relative to MS
- Requires relatively large sample amounts

2. Infrared (IR) and Raman Spectroscopy

IR and Raman spectroscopy are vibrational spectroscopic techniques used for functional group identification and formulation characterization. They are valuable in solid-state analysis, polymorph differentiation, and counterfeit detection.

Mass Spectrometry and Hyphenated Techniques

1. Mass Spectrometry (MS)

Mass spectrometry is a core analytical technique that provides accurate mass, fragmentation patterns, and molecular structure. Recent instruments such as Orbitrap and time-of-flight (TOF) offer high resolution and mass accuracy.

2. Hyphenated Techniques

Combining separation with detection enhances analytical power

- **LC-MS (Liquid Chromatography-Mass Spectrometry):** Widely used for trace analysis, pharmacokinetics, and metabolite identification.
- **GC-MS (Gas Chromatography-Mass Spectrometry):** Ideal for volatile compound analysis with structural confirmation.
- **CE-MS (Capillary Electrophoresis-Mass Spectrometry):** Useful for charged analytes and biopharmaceuticals.

Chemometrics and Multivariate Analysis

The complexity of pharmaceutical data has driven the adoption of chemometrics multivariate statistical tools that extract meaningful patterns from large data sets. Techniques such as principal component analysis (PCA) and partial least squares (PLS) regression enable

- Interpretation of complex spectral data
- Quality control and classification of samples
- Process optimization

Process Analytical Technology (PAT)

PAT frameworks integrate analytical tools into manufacturing processes to ensure product quality in real time. Techniques such as near-IR spectroscopy, Raman, and real-time HPLC enable monitoring reaction progress, blending homogeneity, and critical quality attributes (CQAs). PAT supports Quality by Design (QbD) and continuous manufacturing paradigms.

Emerging Trends in Pharmaceutical Analysis

1. High-Resolution / Accurate-Mass (HRAM) Techniques

HRAM mass spectrometry enables identification of trace impurities and degradation products with high confidence. It also supports metabolomics and proteomics in drug development.

2. Microfluidics and Lab-on-a-Chip

Miniaturized analytical systems reduce sample and reagent consumption. They offer rapid analysis and integration with detection systems for point-of-care testing and high-throughput screening.

3. Artificial Intelligence (AI) in Analytical Interpretation

AI and machine learning algorithms facilitate pattern recognition, predictive modelling, and automated method optimization, transforming data-rich analytical workflows.

Conclusion

Advanced analytical techniques are essential for modern pharmaceutical analysis. They improve sensitivity, specificity, and throughput while reducing time and material costs. Chromatographic, spectroscopic, and mass spectrometric tools especially in hyphenated formats address complex analytical challenges, from impurity profiling to polyspecies quantification. Coupled with chemometrics and integrated PAT approaches, these techniques support robust product development and quality assurance. Continued innovation, particularly in HRAM instrumentation, microfluidics, and AI-enabled analysis, will further enhance pharmaceutical analytics and regulatory compliance.

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Advances in Experimental and Clinical Pharmacology

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Abstract

The field of pharmacology has undergone remarkable transformation over the past two decades, driven by technological innovations and deeper understanding of biological systems. This chapter explores recent advances in both experimental and clinical pharmacology, highlighting the integration of cutting-edge technologies such as artificial intelligence, gene editing, and organoid models into drug discovery and development. We examine how modern experimental approaches are reshaping preclinical research, from high-throughput screening platforms to sophisticated in vitro models that better predict human responses. The clinical dimension addresses paradigm shifts in trial design, the rise of precision medicine through pharmacogenomics, and the emergence of novel therapeutic modalities including biologics and RNA-based medicines. Particular attention is given to safety pharmacology advancements and the critical role of therapeutic drug monitoring in personalized patient care. As pharmacological science continues to evolve, the convergence of computational methods, systems biology, and traditional pharmacological principles promises unprecedented opportunities for developing safer and more effective treatments. This chapter synthesizes current knowledge while identifying emerging trends that will shape the future of pharmacological research and clinical practice.

Keywords: experimental pharmacology, clinical pharmacology, precision medicine, drug discovery

Introduction

The landscape of pharmacology has transformed dramatically in recent years, evolving from traditional approaches centered on empirical observation to highly sophisticated, technology-driven methodologies that leverage computational power, genetic insights, and advanced biological models (Smith & Johnson, 2023). This

evolution reflects broader changes in biomedical science, where the integration of diverse disciplines has created new possibilities for understanding drug action and optimizing therapeutic outcomes. The journey from laboratory bench to patient bedside, often termed translational research, has become increasingly complex yet more promising than ever before (Chen et al., 2024).

The traditional boundaries between experimental and clinical pharmacology have become more permeable, with insights from clinical practice informing laboratory research and vice versa. This bidirectional flow of knowledge has accelerated the pace of drug development and improved our ability to predict clinical outcomes from preclinical data (Anderson & Martinez, 2024).

The significance of recent pharmacological advances extends beyond academic interest, touching on critical public health challenges including antimicrobial resistance, chronic disease management, and the need for treatments addressing previously intractable conditions (Kumar & Singh, 2023). As our understanding of disease mechanisms deepens through genomic and proteomic studies, pharmacology has adapted to exploit this knowledge, creating opportunities for interventions that were unimaginable just decades ago. This chapter explores these developments, examining how experimental and clinical pharmacology are evolving to meet contemporary healthcare needs while laying groundwork for future breakthroughs.

Revolutionary Approaches in Experimental Pharmacology

The experimental pharmacology landscape has been revolutionized by the introduction of three-dimensional cell culture systems and organoid technology, which provide substantially more physiologically relevant models than traditional two-dimensional cultures (Zhang et al., 2024). Organoids, self-organizing three-dimensional structures derived from stem cells or tissue fragments, recreate key aspects of organ architecture and function, enabling researchers to study drug responses in systems that more closely mimic human biology (Miller & Brown, 2023). These models have proven particularly valuable for investigating tissue-specific drug toxicity, understanding disease mechanisms, and testing potential therapeutics in a personalized medicine context where patient-derived organoids can guide treatment selection.

Artificial intelligence and machine learning have emerged as transformative forces in drug discovery, fundamentally altering how researchers identify promising drug candidates and predict their behavior (Harrison et al., 2024). These computational approaches can analyze vast datasets encompassing chemical structures, biological pathways, and clinical outcomes to identify patterns invisible to human researchers. Deep learning algorithms have demonstrated remarkable success in predicting molecular properties, optimizing drug-like characteristics, and even designing entirely novel chemical entities with desired pharmacological profiles (Lee & Park,

2023). The integration of AI extends beyond initial discovery into drug repurposing efforts, where machine learning models identify new therapeutic applications for existing medications, potentially shortening development timelines significantly (Wang et al., 2024).

Gene editing technologies, particularly CRISPR-Cas9 systems, have revolutionized the validation of drug targets and the creation of disease models (Garcia & Lopez, 2023). The precision with which researchers can now modify specific genes allows for unprecedented clarity in establishing causal relationships between molecular targets and disease phenotypes. This capability has proven invaluable in identifying which targets are most likely to yield clinically meaningful benefits when modulated by drugs (Patel et al., 2024).

High-throughput and phenotypic screening technologies have evolved to accommodate increasingly complex biological questions while processing thousands of compounds simultaneously (Morrison & Taylor, 2023). Modern screening platforms incorporate sophisticated detection methods, automated liquid handling, and advanced data analytics to identify compounds with desired activities across diverse assay formats. The shift toward phenotypic screening, where compounds are tested in cellular or organismal contexts without predetermined molecular targets, has yielded drugs acting through novel mechanisms that might have been missed by traditional target-based approaches (Bennett et al., 2024). This renaissance in phenotypic drug discovery reflects growing appreciation for the complexity of biological systems and the limitations of overly reductionist screening strategies.

Clinical Pharmacology: Modern Paradigms and Practices

Clinical trial design has undergone substantial evolution with the adoption of adaptive designs that allow modifications based on accumulating data without compromising trial integrity (Richardson et al., 2024). These flexible approaches enable researchers to adjust sample sizes, modify treatment arms, or enrich enrollment with patients most likely to benefit, potentially accelerating development timelines and reducing costs. Platform trials, where multiple interventions are evaluated within a single trial infrastructure, have demonstrated particular utility in rapidly evolving therapeutic areas and emergency situations such as the recent pandemic response (Foster & White, 2023). Master protocols including basket and umbrella trials leverage biomarker-driven patient selection to evaluate targeted therapies more efficiently than traditional trial designs.

Pharmacogenomics has transitioned from research curiosity to clinical reality, with genetic testing now guiding drug selection and dosing for numerous medications across therapeutic areas (Newman & Clark, 2024). The identification of genetic variants affecting drug metabolism, transport, and target interactions has illuminated much of the previously unexplained variability in drug response observed among

patients. Clinical implementation of pharmacogenomic testing has improved outcomes in areas such as oncology, where tumor genomic profiling informs treatment selection, and psychiatry, where genetic information guides antidepressant choice (Sullivan et al., 2023).

Therapeutic drug monitoring has been enhanced by technological innovations enabling more frequent, less invasive sampling coupled with rapid analytical techniques (Campbell et al., 2024). Point-of-care devices and wearable biosensors are beginning to enable continuous monitoring of drug concentrations, potentially allowing real-time dosing adjustments that maintain therapeutic levels while minimizing toxicity. Population pharmacokinetic modeling approaches incorporate patient-specific factors including genetics, disease state, and concurrent medications to predict optimal dosing regimens for individuals (Morris & Evans, 2023).

Real-world evidence derived from electronic health records, insurance claims, and patient registries increasingly complements traditional clinical trial data in understanding drug performance across diverse patient populations (Hayes & Cooper, 2024). These large datasets capture treatment patterns, outcomes, and adverse events in routine clinical practice, providing insights into drug utilization, effectiveness in populations often excluded from trials, and long-term safety profiles. Regulatory agencies have begun incorporating real-world evidence into approval and labeling decisions, recognizing its value in characterizing drug performance beyond controlled trial settings (Peterson & Wright, 2023). However, methodological challenges in analyzing observational data require careful consideration to avoid biased conclusions that could mislead clinical decision-making.

Novel Therapeutic Modalities and Their Pharmacological Implications

Monoclonal antibodies and related biologics have revolutionized treatment across numerous disease areas, from oncology and immunology to infectious diseases (Edwards & Mitchell, 2024). Pharmacological considerations unique to biologics include immunogenicity, which can affect safety and efficacy, and complex pharmacokinetic profiles influenced by target-mediated drug disposition and other mechanisms distinct from small molecules.

RNA-based therapeutics, including small interfering RNA and messenger RNA technologies, have emerged as powerful new treatment modalities capable of modulating disease-associated targets previously considered undruggable (Collins & Murphy, 2024). The rapid development and deployment of mRNA vaccines demonstrated the potential of this platform technology, while therapeutic applications targeting genetic diseases, cancer, and cardiovascular conditions advance through clinical development. Delivery systems protecting RNA molecules from degradation while facilitating cellular uptake represent critical enabling technologies for this therapeutic class (Lewis & Harris, 2023). Pharmacological

challenges include optimizing tissue targeting, controlling duration of effect, and managing immune responses to both the RNA molecules and their delivery vehicles.

These approaches harness living cells as therapeutic agents or permanently modify patient genomes to correct disease-causing mutations. CAR-T cell therapies for hematologic malignancies exemplify the transformative potential of cellular therapeutics, while gene therapies for inherited disorders demonstrate the feasibility of addressing disease root causes (Anderson et al., 2023).

Targeted protein degradation strategies, particularly proteolysis-targeting chimeras, exploit cellular protein disposal machinery to eliminate disease-associated proteins (Martinez & Robinson, 2024). This approach offers potential advantages over traditional inhibition, including the ability to target proteins lacking enzymatic active sites and achieving sustained target elimination from substoichiometric drug concentrations. As this field matures, understanding tissue-specific degradation efficiency, managing potential off-target protein degradation, and optimizing degrader properties for different target classes remain active areas of investigation.

Safety Pharmacology and Risk Assessment

Advances in toxicology screening have enhanced the ability to identify potential safety liabilities early in drug development, potentially reducing late-stage attrition due to unexpected toxicity (Phillips & Stewart, 2024). High-content imaging approaches enable detailed characterization of cellular responses to compounds, revealing subtle toxicological changes that might herald clinically significant adverse effects. Integration of multiple in vitro assays, computational toxicology predictions, and strategic in vivo studies creates a comprehensive safety assessment paradigm that balances animal welfare considerations with the need for robust safety data.

Pharmacovigilance has been transformed by digital technologies enabling more comprehensive and timely detection of adverse drug reactions (Graham & Nelson, 2024). Regulatory agencies increasingly leverage these tools for post-market surveillance, enabling more rapid responses to emerging safety issues and more nuanced understanding of benefit-risk profiles across diverse patient populations.

Drug interaction studies have become more sophisticated with improved understanding of mechanisms underlying both pharmacokinetic and pharmacodynamic interactions (Morgan & Patterson, 2024). In vitro systems characterizing drug effects on metabolic enzymes and transporters inform clinical interaction study designs and help predict consequences of drug combinations not yet tested in patients. The increasing complexity of modern pharmacotherapy, with patients frequently taking multiple medications simultaneously, elevates the importance of interaction assessment and management (Brooks & Coleman, 2023). Clinical decision support systems incorporating drug interaction databases help

prescribers navigate these complexities, though they must balance sensitivity in detecting potential interactions against the practical need to avoid excessive warnings that may be ignored.

Future Horizons in Pharmacological Science

These methodologies map intricate networks of molecular interactions underlying disease processes, identifying intervention points that may be more effective than targeting individual molecules in isolation. Polypharmacology, once viewed as an undesirable source of side effects, is being reconsidered as a potential advantage when properly harnessed to modulate multiple disease-relevant targets simultaneously (Kim & Lee, 2024). Computational models integrating diverse biological data types enable prediction of drug effects at systems levels, potentially identifying therapeutic opportunities and liabilities not apparent from traditional reductionist approaches.

Machine learning models trained on clinical trial data can identify patient subgroups most likely to benefit from experimental treatments, potentially enabling more efficient trials and better-targeted therapies. AI-driven approaches to analyzing real-world data promise to extract maximal value from the growing volumes of healthcare information being generated, transforming it into actionable insights for improving drug development and clinical care (Fisher & Young, 2023). As these technologies mature, addressing challenges around data quality, model interpretability, and ethical considerations will be essential for realizing their full potential.

The convergence of pharmacology with emerging technologies including nanotechnology, synthetic biology, and quantum computing creates both opportunities and challenges for the field (Morrison & Baker, 2024). Nanoscale drug delivery systems offer unprecedented control over drug distribution and release, potentially enabling therapies for diseases currently constrained by delivery limitations. Synthetic biology approaches may enable creation of entirely new therapeutic modalities, while quantum computing could revolutionize computational drug design by solving molecular problems intractable for classical computers (Allen & Scott, 2023). Navigating this rapidly evolving landscape will require pharmacologists to engage with diverse disciplines while maintaining focus on the fundamental goal of developing safe and effective treatments for patients.

Conclusions

The advances in experimental and clinical pharmacology reviewed in this chapter reflect a field undergoing profound transformation, driven by technological innovation and evolving understanding of biological systems. The integration of sophisticated experimental models, computational approaches, and clinical insights has created unprecedented opportunities for developing more effective and personalized treatments. As pharmacology continues to evolve, maintaining focus

on translating these scientific advances into tangible benefits for patients remains paramount, requiring continued collaboration across disciplines and sustained commitment to rigorous scientific inquiry.

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Zero-Waste Manufacturing of Oral Solid Dosage Forms: A Review of Green Technologies and Process Innovations

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Abstract

The review highlights that solid oral dosage forms (SODFs) dominate pharmaceutical production and thus offer the greatest opportunity for implementing zero-waste strategies, beginning with the substitution of conventional synthetic excipients by biodegradable, plant-derived polymers such as starch, gums, agar and pectin that function as binders, disintegrants, thickeners and gelling agents while reducing toxicity and energy consumption. At the API level, green-chemistry principles—high atom economy, safer solvents (water, ethanol, supercritical CO_2) and catalytic processes—are emphasized to lower the E-factor and eliminate waste-intensive purification steps. Co-processed excipients (e.g., microcrystalline cellulose + colloidal silica) integrate multiple functionalities into a single material, streamlining formulation, decreasing unit operations, and cutting energy use and material loss. Continuous manufacturing and direct-compression processes further enhance material efficiency by eliminating intermediate storage, reducing

start-up/shut-down waste and enabling real-time monitoring through PAT and QbD tools (NIR, Raman, chemometrics). Emerging technologies such as 3-D printing (FDM, SLS) and microfluidics allow on-demand, layer-by-layer tablet fabrication with minimal scrap, while smart-factory IoT sensors and edge analytics support predictive maintenance and demand-supply matching. Sustainable secondary processing is addressed through biodegradable or recyclable packaging materials (PLA, PHA, rPET) and design-for-recycling strategies, complemented by reverse-logistics and circular-supply-chain models that recover unused tablets, packaging and active ingredients. The authors note that high upfront capital costs, technology readiness gaps, fragmented regulatory frameworks and limited stakeholder coordination remain major barriers to widescale adoption of these zero-waste solutions.

Introduction

Growing environmental concerns, regulatory challenges, and the global resolve to decrease industrial waste are all driving the pharmaceutical industry's transformation toward sustainability. Since solid oral dosage forms (SODFs), such as tablets and capsules, are the most produced and consumed type of dosage form, they should be a primary focus of zero waste initiatives. In pharmaceutical manufacturing, the zero-waste idea seeks to reduce resource usage, do away with waste production, and encourage circularity throughout the product lifetime. Zero Waste is defined as “a system to design and management of products and processes for waste removal and material retention and rehabilitation, not burning or burying.” [1]

Starting with the selection and optimization of raw materials and excipients, this review investigates how zero-waste concepts might be included in the production of SODFs. Reducing the environmental impact at the formulation stage requires the use of recyclable or biodegradable excipients, efficient materials, and sustainable procurement. [2] Technological developments in manufacturing, including additive manufacturing, continuous manufacturing, and process intensification, present encouraging opportunities to improve sustainability without sacrificing product quality or legal compliance.

Since systems provide real-time control, predictive maintenance, and energy-efficient operations, process monitoring and optimization are essential to reaching zero waste. Methods-like Quality by Design (QbD) and Process Analytical Technology (PAT) are crucial for reducing resource waste and unpredictability. After primary manufacturing, we must also follow sustainable practices during secondary processing stages like packaging, labeling, and distribution. Waste reduction throughout the supply chain is greatly aided by developments in reverse supply chain models, eco-friendly packaging materials, and logistics optimization.[3]

Considering the possible advantages, a number of obstacles stand in the way of the adoption of zero-waste solutions, such as the high initial cost, technological constraints, regulatory complexity, and reluctance to alter conventional industrial setups. A multi-stakeholder strategy that combines industrial cooperation, academic research, and policy backing is needed to address these obstacles.[4]

The goal of this review is to present a thorough analysis of the methods, new developments, and possible paths for the sustainable production of SODFs. It aims to motivate researchers, producers, and legislators toward a more powerful and ecologically conscious pharmaceutical industry by outlining important strategies, challenges, and suggestions. [5]

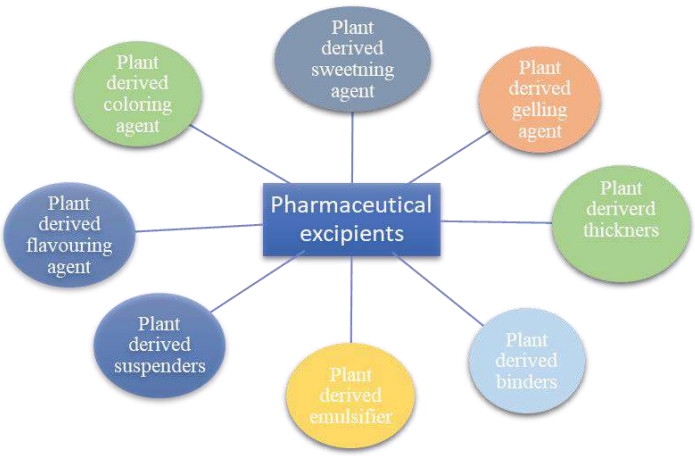
Zero Waste Strategies in Raw Materials and Excipients

- **Sustainable Sourcing and Excipient Selection**

Traditional synthetic excipients raise sustainability concerns due to their non-biodegradable nature, accumulation in ecosystems, and high energy demand during production. In response, the pharmaceutical industry is embracing sustainable alternatives aligned with green chemistry principles that maintain or enhance excipient performance.[6] Although the initial transition costs can be high, eco-friendly excipients ultimately reduce operating expenses, improve market competitiveness, and minimize environmental impact.

- **Bio-Based Excipients**

Plant-derived polymers such as starch, gums, mucilage, and gelatin have expanded rapidly in use as binders, thickeners, film formers, and stabilizers. Their biocompatibility, biodegradability, low toxicity, and cost-effectiveness make them viable alternatives to synthetic materials. They are also applied across cosmetics, textiles, paints, and food industries for their binding and thickening properties.[7]



1. Plant-Derived Thickeners

Polysaccharides like starch, agar, alginates, carrageenan, guar gum, acacia, xanthan, gelatin, pectin, and tragacanth serve as binders, thickeners, gelling agents, and coating materials. Their water-binding capacity and hydrogen-bonding enable controlled-release formulations such as nanohydrogels, implants, and microparticles synthetic agents.[8] Their broad industrial use reflects their functional versatility and eco-friendliness. Natural gums (okra, Abelmoschus, Albizia) perform effectively as disintegrants and binders, often surpass nature.

2. Plant-Derived Binders

Water-processable binders like PAA, CMC, and PVA are safer than fluorinated types but still have performance limits. Bio-based binders lignin, chitosan, and alginate offer renewable, biodegradable options with functional groups (─OH, ─NH_2, ─COOH) that enhance adhesion and elasticity.[9] Their water solubility eliminates the need for toxic organic solvents, supporting cleaner and safer production.

3. Plant-Derived Emulsifiers

Emulsifiers enable the uniform dispersion of fats in water. Natural examples include gum acacia, an acidic polysaccharide from Acacia trees, used as an emulsifier, suspending agent, and binder. Broader natural sources, such as soybeans, oats, milk, and fruits, yield biodegradable, cost-effective, and nutritionally beneficial emulsifiers favored for their clean-label status.[10] Combining plant polysaccharides, proteins, and phospholipids can further stabilize emulsions and enhance performance.[11]

4. Plant-Derived Suspenders

Plant-based suspending agents (gum acacia, tragacanth, guar gum) act as hydrocolloids that stabilize suspensions by forming viscous, three-dimensional networks that slow sedimentation.[12] Materials like xanthan gum and sodium CMC show pseudoplastic (shear-thinning) behavior, stable at rest but fluid under stress, ensuring uniform dosage and usability. Their biodegradability and rheological adaptability make them efficient substitutes for synthetic stabilizers.[13]

5. Plant-Derived Flavoring Agents

Natural flavor compounds—terpenes (limonene), phenolics (eugenol), and aldehydes (vanillin)—offer authentic sensory profiles but vary due to plant growth conditions. Challenges include volatility, oxidation, and microbial contamination.[14] Stability and consistency are improved through microencapsulation, antioxidant use, controlled temperature, and chromatographic profiling. Manufacturers often blend multiple sources and use carriers that stabilize and protect flavor molecules, ensuring safe, consistent quality.

6. Plant-Derived Coloring Agents

Natural pigments like carotenoids, anthocyanins, and betalains deliver vivid coloration and antioxidant benefits in foods, cosmetics, and pharmaceuticals. However, they are sensitive to light, heat, and pH, and have lower chroma than synthetic dyes. Stabilization techniques—microencapsulation, inclusion complexes, and protective additives—preserve color intensity and shelf stability.[15] The trend reflects consumer demand for natural, health-supportive, clean-label ingredients.

Green Chemistry Principles in API Synthesis

Green Chemistry in Active Pharmaceutical Ingredient (API) synthesis re-designs reactions to minimize waste and hazards, aligning with zero-waste objectives.[16] It focuses on atom economy, safer solvents, catalytic efficiency, and reduced purification steps, transforming pharmaceutical production into a sustainable process.

1. Atom Economy and Waste Minimization

High atom-economy reactions, where nearly all atoms of reactants are incorporated into the final product, reduce by-products. Strategies such as rearrangements and addition reactions lower environmental impact and cut disposal costs. Designing reactions that inherently prevent waste aligns perfectly with sustainable manufacturing.[17]

2. Safer Solvents and Reagents

Replacing hazardous organic solvents with greener alternatives like supercritical CO_2, ethanol, and water minimizes toxicity and VOC emissions. These solvents are biodegradable, easier to recover, and safer for workers. They simplify waste-stream management and create cleaner production environments.

3. Catalysis

Catalysis substitutes stoichiometric reagents with recyclable catalysts metal complexes, organocatalysts, and enzymes which perform the same transformations with minimal waste. Catalysis improves atom economy, selectivity, and energy efficiency, cutting purification requirements and emissions. This proactive waste prevention is central to sustainable API production.

4. Link to Dosage Forms

Cleaner API synthesis improves later formulation stages. Fewer process impurities mean reduced need for purification methods such as recrystallization or chromatography. Green-synthesized APIs interact less with excipients, exhibit higher stability, and simplify dosage form development, ensuring efficient, eco-friendly pharmaceutical pipelines from synthesis to final product.[18]

Co-Processed and Multi-Functional Excipients

Co-processed excipients merge multiple conventional excipients through methods like co-spray-drying or co-granulation to produce multifunctional materials with synergistic properties. Unlike simple mixtures, they integrate complementary functionalities—improving manufacturability and sustainability.

For instance, combining microcrystalline cellulose (MCC) with colloidal silica produces a direct-compression excipient that retains MCC's compressibility while improving moisture resistance and flow. Such materials streamline production, reduce tablet defects, and enhance overall product quality.

Manufacturing Efficiency and Waste Reduction

By consolidating several roles into one material, co-processed excipients decrease the number of separate ingredients needed. This simplifies inventory control, raw-material handling, and packaging, while cutting process steps such as granulation, drying, and milling. The results are lower energy use, less cleaning effort, reduced solvent consumption, and diminished process waste—key features of a zero-waste production system.[19]

Performance and Sustainability Advantages

Co-processed excipients improve flowability and compressibility, ensuring uniform die filling and reducing defects like capping or weight variation. This leads to higher first-pass yields, fewer rejected batches, and conservation of both materials and energy. The resulting improvements in consistency and resource efficiency directly reinforce waste-reduction objectives.

Case Example: Ludiflash®

Ludiflash®, a multifunctional excipient for orally disintegrating tablets (ODTs), demonstrates how co-processing enhances formulation efficiency.[20] In granisetron HCl ODTs, Ludiflash combined with sodium starch glycolate achieved rapid disintegration (24–55 s) and near-complete drug release within 15 minutes. The optimal formulation (F6) showed balanced disintegration (38 s), hardness (3.78 kg cm^{-3}), and assay uniformity (99 %). The study concluded that Ludiflash enables rapidly disintegrating, patient-friendly dosage forms while minimizing formulation complexity and material waste.

Sustainable Manufacturing Technologies for Solid Dosage Forms

The pharmaceutical industry is increasingly embracing sustainable technologies to address environmental imperatives while maintaining product quality and efficacy. These innovations optimize resource utilization, minimize waste, and reduce carbon footprints across the lifecycle of solid dosage forms. Key advancements include 3D printing, continuous manufacturing (CM), green chemistry, process analytical technology (PAT), quality by design (QbD), artificial intelligence (AI), and sustainable packaging.[21]

1. Continuous Manufacturing

Superiority Over Batch Processing Continuous manufacturing (CM) confers substantial advantages in material efficiency, energy conservation, and waste minimization relative to traditional batch methodologies, particularly in the fabrication of solid dosage forms via continuous direct compression. This approach facilitates environmentally sustainable production through consistent, real-time controlled operations.[22] Material efficiency is markedly improved through integrated workflows that eliminate intermediate storage and transfer steps, thereby reducing losses inherent in batch systems. Real-time monitoring permits instantaneous adjustments, minimizing substandard output. Energy consumption is substantially reduced owing to steady-state operation, which obviates the energy surges associated with intermittent start-stop cycles in batch processing. Prolonged operational continuity with minimal intervention further enhances resource conservation. Start-up and shutdown waste is significantly curtailed, as CM systems attain steady-state conditions rapidly, in contrast to batch processes wherein calibration phases engender material losses. This conservation of resources aligns with sustainable manufacturing principles. Continuous direct compression integrates active pharmaceutical ingredient (API) synthesis with final formulation, minimizing process interruptions and material handling losses, thereby supporting zero-waste objectives. PAT facilitates continuous material flow monitoring and quality assurance.[21] CM is consonant with broader sustainability paradigms, including circular economy models and Industry 4.0 integration, promoting resource preservation and operational efficiency.[22] Collectively, these attributes position CM as a cornerstone for environmentally responsible pharmaceutical manufacturing.

2. Advanced Particle Engineering and Energy

Efficient Drying for Zero-Waste Production. The imperative for zero-waste pharmaceutical manufacturing underscores the critical role of advanced particle engineering and innovative drying technologies in reducing solvent utilization, energy demands, and environmental impact in solid dosage form production.[23] Solvent-free methodologies, including hot melt extrusion (HME), dry granulation via roller compaction, and mechanochemical activation, eliminate or substantially reduce reliance on organic solvents, thereby mitigating environmental pollution, energy-intensive solvent recovery, and hazardous waste generation, in accordance with green chemistry tenets.

Hot Melt Extrusion (HME)

A continuous, solvent-free process involving thermal blending of pharmaceutical constituents into a molten phase, subsequently shaped into tablets, pellets, or films. HME is particularly efficacious in generating amorphous solid dispersions to enhance the bioavailability of poorly water-soluble APIs.[24] It enables precise

modulation of drug release kinetics and minimizes waste and energy expenditure. Thermal degradation of heat-labile compounds necessitates rigorous formulation and process optimization.

Dry Granulation (Roller Compaction)

Involves high-pressuresion of powder blends into ribbons or sheets, followed by milling into granules suitable for tableting or encapsulation. This solvent-free technique obviates drying requirements, rendering it ideal for moisture-sensitive APIs and excipients. It streamlines processing, reduces operational costs, and minimizes material losses. Compatibility with continuous manufacturing and scalability further augment its sustainability profile; however, granule uniformity demands optimization to ensure consistent product quality.

Mechanochemical Activation

Harnesses mechanical energy through milling or grinding to induce solid-state transformations, such as amorphization or co-crystal formation, thereby enhancing solubility, dissolution, and bioavailability without solvent intervention. Its versatility across diverse APIs supports sustainable formulation development, though high energy inputs necessitate the adoption of energy-efficient milling systems to align with zero-waste goals.[25] Green solvent technologies substitute conventional hazardous solvents with environmentally benign alternatives to foster sustainable drug formulation.

- **Organic Solvent-Free Liquid Chromatography:** Employs mixed-micellar mobile phases for stability-indicating assays (e.g., remdesivir), validated for drug content and impurity profiling with reduced ecological impact.[26]
- **Green High-Performance Liquid Chromatography (HPLC):** Incorporates mobile phase recycling to enable simultaneous multi-analyte determination, significantly lowering solvent consumption, analytical duration, and costs while adhering to green analytical chemistry principles
- **Supercritical Fluid Technology (SFT):** Utilizes supercritical carbon dioxide as a green solvent to enhance drug solubility with scalability and minimal environmental footprint, albeit requiring specialized equipment and precise parameter control.[27]
- **Agro-Waste-Derived Solvents:** Aqueous extracts of agro-waste ash function as in situ bases and homogeneous catalysts, exemplifying resource-efficient, eco-compatible reaction media
- **Dry Coating Techniques:** Solvent-free approaches such as hot-melt and press coating enhance product stability, eliminate toxicological and environmental concerns associated with solvent-based coating, and reduce production costs. Energy-efficient drying modalities, notably microwave vacuum drying (MVD), are instrumental in achieving zero-waste objectives by substantially reducing

processing time and energy consumption while preserving product integrity. MVD integrates microwave heating within a vacuum environment, achieving up to 86.2% reduction in drying time and 62.2% in energy use compared to conventional hot air drying, while enhancing bioactive retention.[28] It is particularly advantageous for thermolabile materials, attaining energy efficiencies up to 80% without inducing defects.[29] Pulsed MVD optimizes energy delivery through intermittent power application, yielding superior efficiency and product quality relative to continuous modes. These technologies collectively diminish carbon emissions, enhance process efficiency, and support sustainable manufacturing imperatives.

Emerging Technologies

Additive manufacturing (3D printing) and microfluidics constitute transformative platforms for zero-waste, sustainable production of solid dosage forms through precision engineering and minimal resource utilization. Techniques such as selective laser sintering (SLS) and fused deposition modeling (FDM) enable layer-by-layer construction of customized tablets with complex architectures, eliminating mold requirements and minimizing material waste.[30] On-demand fabrication mitigates overproduction and inventory-related losses. Microfluidics affords exquisite control over microscale fluid dynamics, facilitating high-throughput formulation screening and microfabrication with drastically reduced raw material consumption.[31] It enables precise engineering of controlled-release drug delivery systems, enhancing therapeutic efficacy and patient adherence. Synergistic integration of 3D printing and microfluidics advances personalized medicine by enabling patient-specific dosage forms, optimizing material utilization, and reducing waste from standardized mass production. ML-driven optimization of process parameters further minimizes energy consumption and emissions in additive manufacturing, establishing benchmarks for sustainable industrial practice. In conclusion, the confluence of continuous manufacturing, solvent-free particle engineering, green solvent systems, energy-efficient drying, and emerging digital technologies propels the pharmaceutical sector toward zero-waste, resource-efficient, and environmentally responsible manufacturing paradigms, ensuring therapeutic excellence while safeguarding ecological integrity. systems, enhancing therapeutic efficacy and patient. Synergistic integration of 3D printing and microfluidics advances personalized medicine by enabling patient-specific dosage forms, optimizing material utilization, and reducing waste from standardized mass production. ML-driven optimization of process parameters further minimizes energy consumption and emissions in additive manufacturing, establishing benchmarks for sustainable industrial practice [32][33]. In conclusion, the confluence of continuous manufacturing, solvent-free particle engineering, green solvent systems, energy-efficient drying, and emerging digital technologies propels

the pharmaceutical sector toward zero-waste, resource-efficient, and environmentally responsible manufacturing paradigms, ensuring therapeutic excellence while safeguarding ecological integrity.

Process Monitoring and Optimization for Zero Waste

Process Analytical Technology (PAT) and Real-Time Release Testing (RTRT)

Process Analytical Technology (PAT) is an FDA-endorsed framework that facilitates the design, analysis, and regulation of pharmaceutical production by means of fast, in-process measurements of key process parameters (CPPs) and critical quality attributes (CQAs) to ensure the quality of the final product.

It enables real-time release and continuous improvement by switching production from static batch processes to a dynamic, real-time control method.[34] Reduced batch and raw material losses, decreased scrap rates, improved safety through automation, quicker scale-up, and increased asset utilization are some of the main advantages, all of which contribute to better product quality, patient safety, and profitability. Implementation encounters both external (vendor incompatibility, differing regulatory requirements) and internal (uncertain ROI, competence gaps, system integration) obstacles.

Near infrared reflectance measurement, and other analytical instruments are employed by PAT and can be used in off-line, at-line, on-line, or in-line modes.[6] A standard PAT workflow includes the following steps: choosing an appropriate unit operation; determining whether it can be carried out at lab scale; analyzing the cost-benefit ratio; selecting a technique (usually NIR due to its speed and non-destructive nature); integrating the probe or sampling system; and creating a calibrated chemometric model that is connected to a reference method.

Aspect	Description
Definition	System for designing, analyzing, and controlling manufacturing via CPP/CQA measurements
Main Benefits	Reduced waste, real-time release, higher safety, faster scale-up, better profitability
Common Tools	NIR, Raman, mid-IR, MS, chromatography, FBRM, etc., in-line/at-line modes
Implementation Steps	Unit-operation selection → feasibility → cost-benefit → technique choice → integration → model development
Barriers to Adoption	ROI uncertainty, skill gaps, hardware/software integration, regulatory differences

Zero Waste in Secondary Processing and Supply Chain

Sustainable Pharmaceutical Packaging

1. **Biodegradable, Compostable, and Recyclable Packaging Materials**

- **Biodegradable Materials:** Biodegradable polymers such as polylactic acid (PLA), polyhydroxyalkanoates (PHA), and cellulose derivatives are increasingly used in pharmaceutical packaging. PLA and PHA are derived from renewable sources like corn starch and microbial fermentation, offering excellent biodegradability and mechanical strength.[36] Cellulose-based films are used in blister packs and sachets due to their non-toxic nature and compostability.
- **Compostable Materials:** Compostable packaging materials include starch blends, bagasse (sugarcane fiber), and certain biopolymers like PLA and PHA. These materials decompose under industrial composting conditions and are suitable for trays, inserts, and secondary packaging. Their use reduces landfill burden and supports circular economy principles.[37]
- **Recyclable Materials:** Recyclable materials such as recycled polyethylene terephthalate (rPET), high-density polyethylene (HDPE), polypropylene (PP), and aluminum are widely adopted in pharmaceutical bottles, blister trays, and foils. These materials are compatible with existing recycling infrastructure and help reduce reliance on virgin plastics. Mono-material packaging designs further enhance recyclability by avoiding multi-layer composites.

Minimization of Packaging Waste

- **Design Strategies:** Packaging waste is minimized through right-sizing, lightweight material selection, and elimination of unnecessary secondary packaging. Eco-design principles focus on reducing material usage while maintaining product protection and regulatory compliance.
- **Technological Innovations:** Mono-material packaging simplifies recycling and reduces contamination. Digital printing technologies enable small-batch customization, reducing label waste and inventory surplus. Smart labeling and QR codes can replace paper inserts, further reducing material use.[8]

Dose-Specific and On-Demand Packaging

- **Unit-Dose Packaging:** Unit-dose formats are commonly used in hospitals and clinical settings to ensure hygiene, accurate dosing, and reduced medication waste. These formats also improve patient safety and adherence.
- **Personalized and On-Demand Packaging:** Advancements in 3D printing and smart packaging technologies enable personalized medication delivery and on-demand packaging. These approaches reduce surplus packaging and support

precision medicine. Smart blister packs with embedded sensors can monitor patient adherence and optimize therapy outcomes.[32]

End-of-Life Management and Reverse Logistics (Circular Economy)

The pharmaceutical industry faces increasing pressure to adopt sustainable practices across the product lifecycle, including end-of-life management. Reverse logistics and circular economy principles are critical in handling expired, unused, or recalled medicines and reclaiming packaging materials.[38]

- **Handling of Expired or Recalled Medicines:** Expired and recalled pharmaceuticals pose significant environmental and public health risks if not properly managed. Reverse logistics systems enable the safe return of these products from consumers, pharmacies, and healthcare institutions to manufacturers or authorized disposal facilities. This process typically involves:
- **Collection:** Medicines are retrieved from end-users through take-back programs, pharmacy drop-off points, or hospital returns.
- **Transportation and Storage:** Returned products are securely transported and temporarily stored under controlled conditions to prevent leakage or misuse.
- **Disposal:** Final disposal is conducted in specialized facilities using methods such as high-temperature incineration or chemical neutralization, ensuring compliance with environmental regulations.[39]

Reverse logistics also supports regulatory compliance, resource optimization, and brand reputation. It is increasingly integrated into supply chain strategies to reduce waste and improve traceability.

Reclaiming Materials from Packaging and Unused Products

Where feasible and safe, pharmaceutical companies are exploring the recovery of materials from packaging and unused products. This includes:

- **Recycling of packaging components:** Materials such as aluminum foils, HDPE bottles, and cardboard cartons are separated and recycled through certified channels.
- **Reprocessing of unused medicines:** In some controlled settings, unopened and unexpired medicines may be redirected to humanitarian aid or reprocessed for non-clinical use, subject to strict quality checks.
- **Material recovery technologies:** Innovations in sorting and sterilization allow for the reclamation of high-value packaging components, reducing the demand for virgin materials.

These practices align with circular economy goals by extending the lifecycle of materials and minimizing environmental impact.[40]

Challenges and Barriers to Zero Waste Implementation

Before identifying cross-cutting themes, it is essential to first summarize the primary data and core findings from each distinct study area presented in the source

materials. This provides the foundational evidence for the subsequent analysis by isolating the key statistics, causal relationships, and strategic challenges identified in North Lombok, Sub-Saharan Africa, and the comparative case of China and Germany.[41]

1. Causal Barrier Analysis in North Lombok

A study of the "Zero Waste North Lombok" program by Suci & Rakhmatulloh utilized the fuzzy DEMATEL method to identify and causally rank barriers to success. The analysis, based on input from 8 local stakeholders, provides a quantitative hierarchy of obstacles.

- A total of 12 distinct barriers were identified and analyzed.
- These barriers were categorized into two primary groups: influential (cause) barriers that drive other problems, and receptive (effect) barriers that are influenced by others.
- Four barriers were classified as influential, listed here in descending order of their causal influence (D-R score):
  - Lack of policies and regulations on waste (B2):1.5221
  - Lack of collaboration between stakeholders (B4):0.7273
  - Uncertainty about circular economy targets and strategies (B7):0.7011
  - Inadequate sanctions and fines (B10):0.6589
- The barrier identified as the most receptive (i.e., most influenced by other factors) was Lack of temporary shelters (B8), with a D-R score of -0.7538.
- Lack of environmental awareness (B3) registered the highest interaction value (D+R score of 10.9128), indicating it is a central node influenced by all other identified barriers.[42]

2. Macro-Level Challenges in Sub-Saharan Africa (SSA)

- Waste generation in SSA is increasing rapidly, growing from 125 million tons in 2012 to an anticipated 244 million tons by 2025.
- The typical waste composition in SSA is dominated by organic material: 57% organic, 13% plastic, 9% paper, 4% metal, 4% glass, and 13% other.
- The economic impact of improper waste disposal is substantial. In Ghana, for example, it costs an estimated USD 290 million annually, equivalent to 1.6% of the country's GDP.
- The primary barriers identified at a regional level are consistent with those found elsewhere and include: inadequate policies and regulations, insufficient funding, lack of political will, low capacity of personnel, and an absence of educational programs.[43]

Waste Management Trajectories in China and Germany

The study by Lee et al. provides a comparative look at the waste management strategies and outcomes in China and Germany, illustrating divergent paths and highlighting the impact of different policy frameworks.

Feature	China	Germany
MSW Volume	Increased from 135 million tons (2001) to 228 million tons (2018) in cities.	Total MSW decreased from 35.4 million tons (1990) to 32.5 million tons (2014).
Primary Disposal Method	Primarily landfilling (~60% in 2017), with a rapid shift towards incineration (target of >50% by 2020).	Ban on landfilling untreated MSW since 2005; focus on waste hierarchy.
Recycling Rate	Not specified, but challenges noted with imported waste overwhelming capacity.	67% of MSW is recycled; packaging recycling rates consistently above 80% for most materials except plastic.
Governing Policy Driver	Top-down government plans (e.g., 'Thirteenth Five-Year Plan') and recent bans on plastics and foreign waste.	Legally binding frameworks like the Packaging Ordinance (1991) and Circular Economy Act, based on the 'polluter pays' principle.
Key Challenges	Landfill shortages, environmental contamination from landfills, public resistance to incinerators, and low efficiency of incineration due to high-moisture waste (up to 60% biogenic).	Reaching higher plastic recycling quotas (63% target by 2022), finding alternatives for Refuse-Derived Fuels (RDF) due to coal phase-out, and developing chemical recycling.

This summary of distinct data sets provides the basis for the following section, which will now analyze the compelling patterns that emerge when these findings are considered collectively.

Analysis of Patterns, Correlations, and Anomalies

This section moves beyond summarizing individual data sets to synthesize them, identifying common themes and correlations that emerge when the findings from North Lombok, SSA, and the China-Germany comparison are viewed collectively. This synthesis is crucial for understanding the systemic nature of waste management challenges and validating the central thesis of this analysis.

The Primacy of Policy and Governance Frameworks

A consistent pattern across all three studies points to policy and governance as the most critical factor in the success or failure of waste management systems. This is not just a correlation but a causal relationship identified in the data.

- The North Lombok study quantitatively establishes "Lack of policies and regulations" (B2) as the single most influential barrier, with the highest causal score (D-R of 1.5221). This indicates that failures in this area are the primary driver of subsequent problems in funding, infrastructure, and public behavior.
- This quantitative causal link from North Lombok finds a direct qualitative parallel in the SSA review, which identifies "inadequate policies and regulations" and "lack of political will" as primary hindrances to implementing a circular economy model across the region.
- The German case study provides a powerful counter-example. Its success in achieving high recycling rates and diverting waste from landfills is explicitly grounded in foundational, legally binding policies like the Circular Economy Act and the 'polluter pays' principle established by the Packaging Ordinance. This contrasts sharply with China's challenges, which persist despite top-down initiatives, suggesting that the nature and enforcement of policy are as important as its existence.[44]

Economic Barriers and Insufficient Investment

The recurring theme of financial constraints is another strong pattern, but the data suggests it is often a symptom of weaker governance rather than an independent root cause.

- In North Lombok, "Lack of financial and economic support" (B1) is classified as a receptive barrier. This quantitative finding suggests that financial shortfalls are exacerbated by, and a consequence of, other factors—most notably the lack of a clear policy framework that would attract and direct investment.
- The SSA review highlights "insufficient funding" as a major challenge, noting that a successful transition to a circular economy requires an estimated investment of USD 6 to 42 billion. The scale of this need underscores the role

of government and international policy in creating an investment-friendly environment.

- The China study illustrates how economic factors can drive environmentally poor outcomes even when technical solutions are available. The "high costs of capturing" landfill gases, relative to low profits for their utilization, is cited as a reason why approximately 50% of China's landfills lacked efficient gas collection systems as of 2016. This demonstrates that without supportive economic policies, technically feasible solutions remain unimplemented.[45]

Ultimately, the data shows that financial constraints are not an independent root cause of failure, but rather a predictable outcome of a poorly defined policy environment, reinforcing the primacy of governance.

Data Integrity Anomaly and Methodological Implications

In synthesizing the data, a critical anomaly was identified in the Debrah et al. review paper on Sub-Saharan Africa. The text states that "the SSA waste is expected to increase to 244 billion tons" by 2025. However, the accompanying Figure 1, which plots this projection, explicitly labels its y-axis in "million ton" and shows the 2025 data point at the 244 marks.

This discrepancy of a factor of 1,000 is a significant error. Given the context of the preceding data point (125 million tons in 2012) and the graphical representation, it is clear that the intended figure is 244 million tons. While likely a typographical error, this anomaly impacts the perceived rigor of the source and highlights the importance of critical data verification, even in peer-reviewed literature.[41]

The identification of these patterns and the anomaly set the stage for a closer look at the analytical approaches used in the source materials.

Conclusion

Zero-waste manufacturing represents a transformative step toward sustainable pharmaceutical production. By replacing synthetic excipients with biodegradable, plant-derived polymers and applying green chemistry principles such as atom economy and safer solvents, waste generation is minimized from synthesis to formulation. Co-processed excipients, continuous manufacturing, and 3D printing further enhance efficiency while reducing material loss. Sustainable packaging, reverse logistics, and circular supply chains extend waste reduction beyond production. Despite challenges in cost, regulation, and infrastructure, industry-wide collaboration can enable a circular, efficient, and environmentally responsible pharmaceutical sector that aligns innovation with ecological preservation.

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Healthcare Monitoring Systems Using MANET

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Abstract

The Human Internet of Things (IoT) in healthcare represents an advanced integration of interconnected medical devices, wearable sensors, smart implants, and cloud-based platforms that enable continuous monitoring, analysis, and management of patient health data. By extending traditional Internet of Things (IoT) frameworks into human-centric systems, IoT facilitates real-time communication between patients, healthcare providers, and intelligent decision-support systems. This paradigm enhances personalized medicine, remote patient monitoring, chronic disease management, and emergency response services. The architecture of IoT in healthcare typically consists of multi-layered components, including the perception layer (biosensors and wearable devices), network layer (wireless communication technologies such as Wi-Fi, Bluetooth, and 5G), processing layer (edge and cloud computing platforms), and application layer (healthcare analytics and user interfaces). Integration with emerging technologies such as artificial intelligence (AI), big data analytics, and blockchain further strengthens data-driven clinical decision-making and interoperability across healthcare ecosystems. Despite its transformative potential, IoT faces significant security and privacy challenges. These include data breaches, unauthorized access, device vulnerabilities, insecure communication channels, and lack of standardized security frameworks. Ensuring confidentiality, integrity, and availability of sensitive medical data requires robust encryption mechanisms, secure authentication protocols, intrusion detection systems, and regulatory compliance with healthcare standards. Applications of IoT in healthcare span remote patient monitoring,

telemedicine, smart hospitals, elderly care systems, fitness tracking, and predictive health analytics. By enabling proactive and preventive healthcare models, IoT improves patient outcomes, reduces operational costs, and enhances healthcare accessibility. However, addressing architectural complexities and cybersecurity risks remains critical to achieving sustainable and secure deployment of IoT systems in modern healthcare environments.

Keywords: MANET, Infrastructured, Infrastructure less networks, Pros of Ad-hoc, Cons of Ad-hoc

Introduction

The people's future living environments are emerging based upon information resource provided by the connections of various communication networks for users. New small devices like Personal Digital Assistants (PDAs), mobile phones, handhelds, and wearable computers enhance information processing and accessing capabilities with mobility. Moreover, traditional home appliances, e.g. digital cameras, cooking ovens, washing machines, refrigerators, vacuum cleaners, and thermostats, with computing and communicating powers attached, extend the field to a fully pervasive computing environment. With this in view, modern technologies should be formed within the new paradigm of pervasive computing, including new architectures, standards, devices, services, tools, and protocols. Wireless ad hoc networks are collections of wireless nodes, that communicate directly over a common wireless channel. The nodes are equipped with wireless transceiver. They don't need any additional infrastructure, such as base station or wired access point, etc. Therefore, each node doesn't only play the role of an end system, but also acts as a router, that sends packets to desired nodes. Mobile networking is one of the most important technologies supporting pervasive computing. During the last decade, advances in both hardware and software techniques have resulted in mobile hosts and wireless networking common and miscellaneous. Generally, there are two distinct approaches for enabling wireless mobile units to communicate with each other:

- **Infrastructured**

Wireless mobile networks have traditionally been based on the cellular concept and relied on good infrastructure support, in which mobile devices communicate with access points like base stations connected to the fixed network infrastructure. Typical examples of this kind of wireless networks are GSM, UMTS, WLL, WLAN, etc.

- **Infrastructureless**

As to infrastructureless approach, the mobile wireless network is commonly known as a mobile ad hoc network (MANET). A MANET is a collection of wireless nodes

that can dynamically form a network to exchange information without using any pre-existing fixed network infrastructure. This is a very important part of communication technolog that supports truly pervasive computing, because in many contexts information exchange between mobile units cannot rely on any fixed network infrastructure, but on rapid configuration of a wireless connections on-the-fly. Wireless ad hoc networks themselves

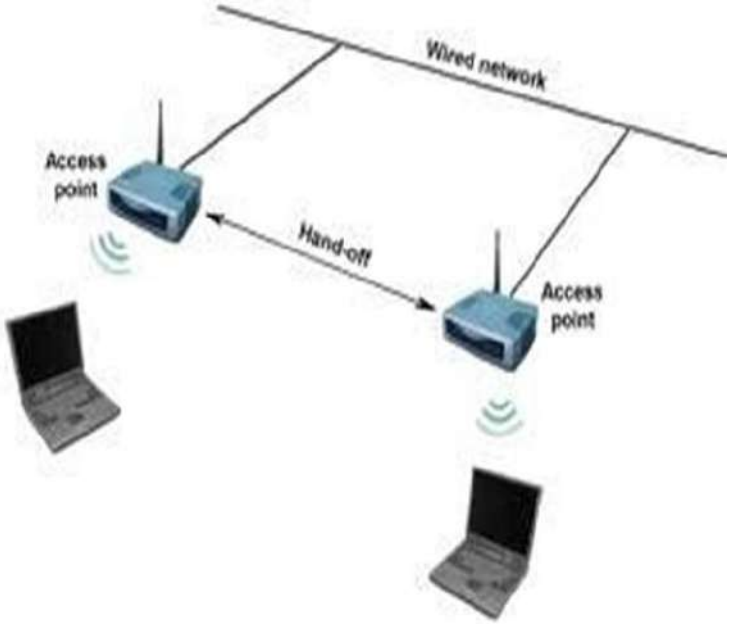


Fig.1 shows the examples of both infrastructured and infrastructureless ad hoc wireless networks.

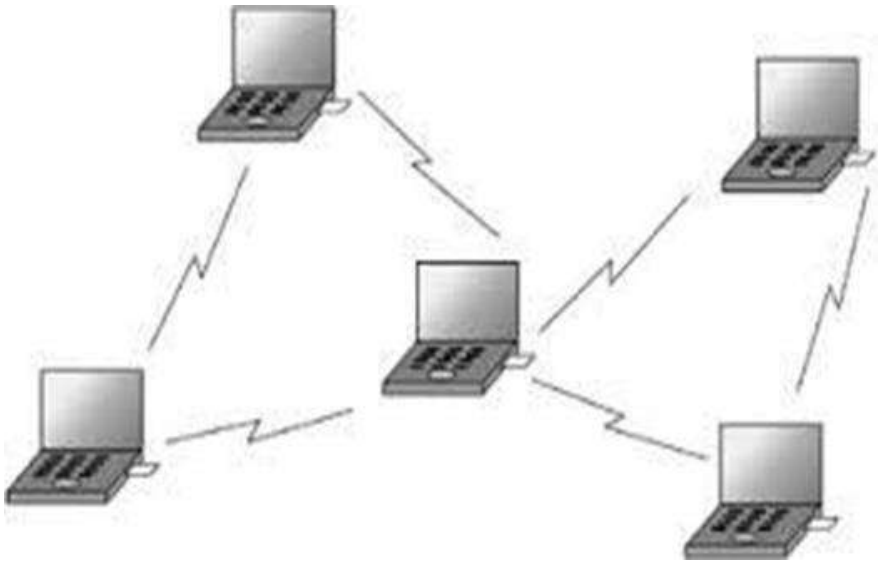


Fig.1 Infrastructure ad hoc wireless networks

Manet Concept

A mobile ad hoc network is a collection of wireless nodes that can dynamically be set up anywhere and anytime without using any pre-existing network infrastructure. It is an autonomous system in which mobile hosts connected by wireless links are free to move randomly and often act as routers at the same time. The traffic types in ad hoc networks are quite different from those in an infrastructured wireless network, including:

i. **Peer-to-Peer:**

Communication between two nodes which are within one hop. Network traffic (Bps) is usually consistent.

ii. **Remote-to-Remote:**

Communication between two nodes beyond a single hop but which maintain a stable route between them. This may be the result of several nodes staying within communication range of each other in a single area or possibly moving as a group. The traffic is similar to standard network traffic.

iii. **Dynamic Traffic:**

This occurs when nodes are dynamic and moving around. Routes must be reconstructed. This results in a poor connectivity and network activity in short bursts.

Classification of Attacks

As previously discussed, we have categorized the presently existing attacks into two broad categories: DATA traffic attacks and CONTROL traffic attacks. This classification is based on their common characteristics and attack goals. For example: Black-Hole attack drops packet every time, while Gray-Hole attack also drops packets but its action is based on two conditions: time or sender node. But from network point of view, both attacks drop packets and Gray-Hole attack can be considered as a Black-Hole attack when it starts dropping packets. So, they can be categorized under a single category.

There are few attacks that have implications on both DATA & CONTROL traffic, so they cannot be classified into these categories easily. So those attacks are left for future discussions.

DATA Traffic Attack

DATA traffic attack deals either in nodes dropping data packets passing through them or in delaying of forwarding of the data packets. Some types of attacks choose victim packets for dropping while some of them drop all of them irrespective of sender nodes. This may highly degrade the quality of service and increases end to end delay. This also causes significant loss of important data. For e.g., a 100Mbps wireless link can behave as 1Mbps connection. Moreover, unless there is a

redundant path around the erratic node, some of the nodes can be unreachable from each other altogether.

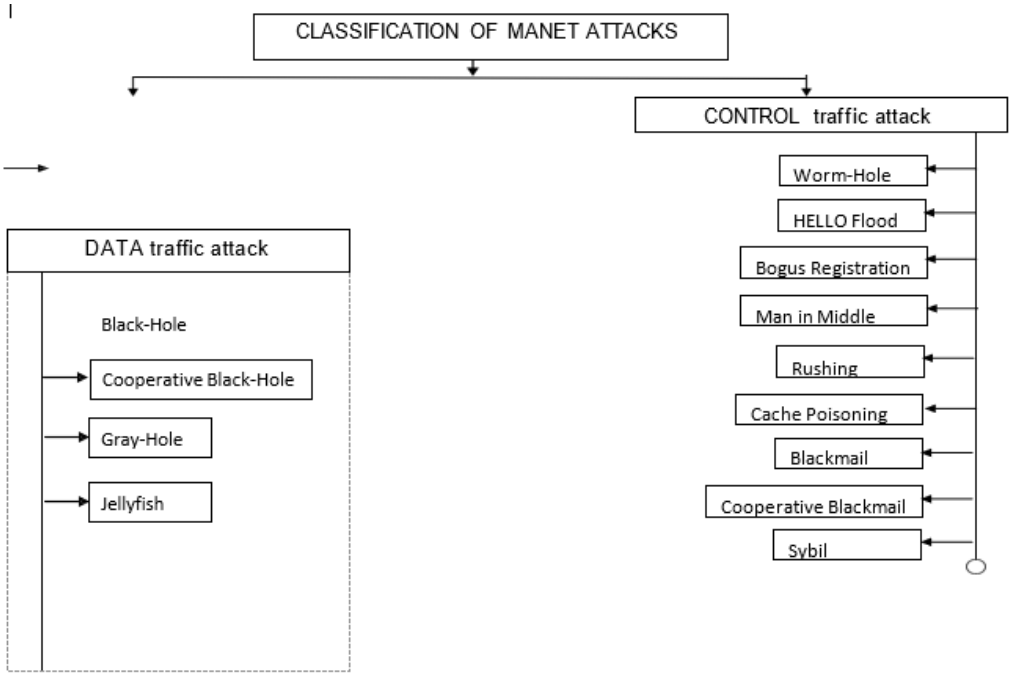


Figure 1: Classification of Mobile ADHOC Network (MANET) attacks

Black-Hole Attack

In this attack, a malicious node acts like a Black hole, dropping all data packets passing through it as like matter and energy disappears from our universe in a black hole. If the attacking node is a connecting node of two connecting components of that network, then it effectively separates the network in to two disconnected components.

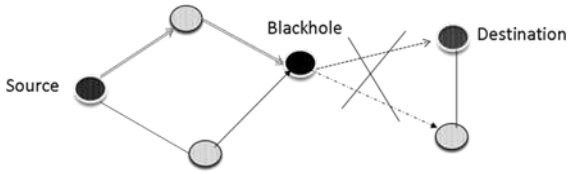


Figure 2: Black-Hole Attack Here the Black-Hole node separates the network into two parts.

Few Strategies to Mitigate the Problem:

- Collecting multiple RREP messages (from more than two nodes) and thus hoping multiple redundant paths to the destination node and then buffering the packets until a safe route is found.
- Maintaining a table in each node with previous sequence number in increasing order. Each node before forwarding packets increases the sequence number.

The sender node broadcasts RREQ to its neighbors and once this RREQ reaches the destination, it replies with a RREP with last packet sequence number. If the intermediate node finds that RREP contains a wrong sequence number, it understands that somewhere something went wrong.

Cooperative Black-Hole Attack

This attack is similar to Black-Hole attack, but more than one malicious node tries to disrupt the network simultaneously. It is one of the most severe DATA traffic attacks and can totally disrupt the operation of an Ad Hoc network. Mostly the only solution becomes finding alternating route to the destination, if at all exists.

Detection Method is similar to Ordinary Black- Hole Attack

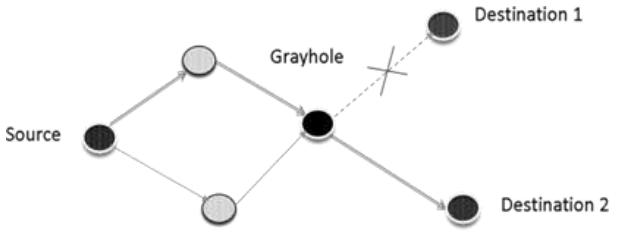
In addition, another solution is securing routing and node discovery in MANET by any suitable protocol such as SAODV, SNRP, SND, SRDP etc. Since each node is already trusted, black hole node should not be appearing in the network.

Gray-Hole Attack

Gray-Hole attack has its own characteristic behavior. It too drops DATA packets, but node's malicious activity is limited to certain conditions or trigger. Two most common type of behavior:

- **Node Dependent Attack:** drops DATA packets destined towards a certain victim node or coming from certain node (fig 3), while for other nodes it behaves normally by routing DATA packets to the destination nodes correctly.
- **Time Dependent Attack:** drops DATA packets based on some predetermined/trigger time while behaving normally during the other instances. (fig. 4)

Detecting this behaviorist attack is very difficult unless there exists a system wide detection algorithm, which takes care of all the nodes performance in the network. Sometimes nodes can interact with each other and can advise malicious nodes existence to other friendly nodes. Approach is similar to Black- Hole attack where sequence number feedback might detect some Gray-Hole attack. If multiple paths exist between sender and destination then buffering packets with proper acknowledgement (for e.g. 2ACK [14]) might detect active Gray-Hole attack in progress. But dormant or triggered attack is difficult to detect with this approach.



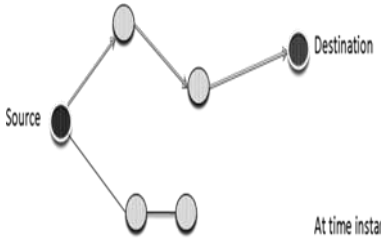


Figure 3: Gray-Hole – Node dependent attack

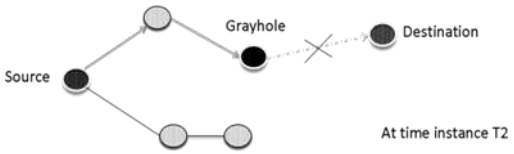


Figure 4: Gray-Hole – Time dependent attack

Jellyfish Attack

Jellyfish attack is somewhat different from Black-Hole & Gray-Hole attack. Instead of blindly dropping the data packets, it delays them before finally delivering them. It may even scramble the order of packets in which they are received and sends it in random order. This disrupts the normal flow control mechanism used by nodes for reliable transmission. Jellyfish attack can result in significant end to end delay and thereby degrading QoS. Few of the methods used by attacker in this attack:

- One of the methods is scrambling packet order before finally delivering them instead of received FIFO order. ACK based flow control mechanism will generate duplicate ACK packets which will unnecessarily consume precious network bandwidth and battery life.
- Another method can be, performing selective Black-Hole attack by dropping all packets at every RTO. This will cause timeout in sender node at every RTO for that duration. If nodes use traffic shaping, default flow control mechanism might be triggered to the sender node as it is same as destination overwhelm
- The attacking node can store all the received packets in its buffer but sends them after some random delay maintaining the received packet order. Here also the flow control mechanism gets confused. Sometimes the source node might take a longer route instead of the most obvious shortest route.

Few of the solutions to Jellyfish type attack includes:

- **2ACK [14]:** The basic idea of the 2ACK scheme is that, when a node forwards a data packet successfully over the next hop, the destination node of the next-hop link will send back a special two-hop acknowledgment called 2ACK to indicate that the data packet has been received successfully. Such a 2ACK transmission takes place for only a fraction of data packets, but not for all.

- **Credit based systems [22]:** This approach provides incentives for successful transmission of some kind of token or credit which the node might use when it starts sending its own packet.
- **Reputation based scheme [22]:** Here individual nodes collectively detect misbehaving nodes (such as CONFIDANT).

CONTROL Traffic Attack

Mobile Ad-Hoc Network (MANET) is inherently vulnerable to attack due to its fundamental characteristics, such as open medium, distributed nodes, autonomy of nodes participation in network (nodes can join and leave the network on its will), lack of centralized authority which can enforce security on the network, distributed co-ordination and cooperation. The existing routing protocols cannot be used in MANET due to these reasons.

Many of the routing protocols devised for use in MANET have their individual characteristic and rules. Two of the most widely used routing protocols is Ad-Hoc on Demand Distance Vector routing protocol (AODV), which relies on individual node's cooperation in establishing a valid routing table and Dynamic MANET On-Demand (DYMO), which is a fast light weight routing protocol devised for multi hop networks. But each of them is based on trust on nodes participating in network. The first step in any successful attack requires the node to be part of that network. As there is no constraint in joining the network, malicious node can join and disrupts the network by hijacking the routing tables or bypassing valid routes. It can also eavesdrop on the network if the node can establish itself as the shortest route to any destination by exploiting the unsecure routing protocols. Therefore, it is of utmost importance that the routing protocol should be as much secure as it can be. Though there can be other kinds of attack, such as jamming attacks, which is not CONTROL attack. They can be tackled as a part of physical layer security protocols. Henceforth those attacks will not be discussed as are out of scope of this paper.

Worm Hole Attack

Worm hole, in cosmological term, connects two distant points in space via a shortcut route. In the same way in MANET also one or more attacking node can disrupt routing by short- circuiting the network, thereby disrupting usual flow of packets. If this link becomes the lowest cost path to the destination, then these malicious nodes will always be chosen while sending packets to that destination. The attacking node. then can either monitor the traffic or can even disrupt the flow (via one of the DATA traffic attacks). Wormhole attack can be done with single node also but generally two or more malicious node connects via a wormhole-link. In figure 5, Node X and Y performing wormhole attack.

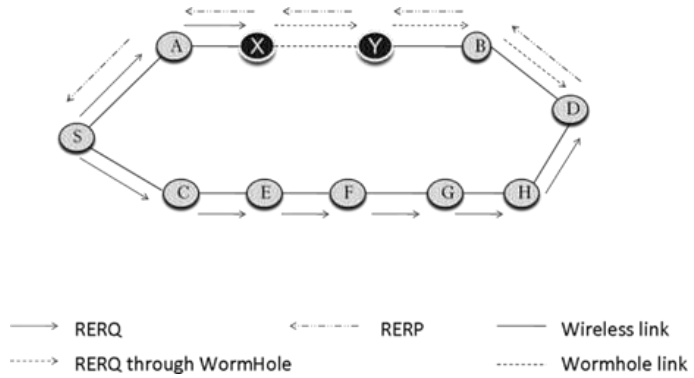


Figure 5: Worm-Hole attack

There have been few proposals recently to protect networks from worm-hole attack:

- **Geographical Leashes & Temporal Leashes:** A leash is added to each packet in order to restrict the distance the packets are allowed to travel. A leash is associated with each hop. Thus, each transmission of a packet requires a new leash. A geographical leash is intended to limit the distance between the transmitter and the receiver of a packet. A temporal leash provides an upper bound on the lifetime of a packet.
- **Using Directional Antenna:** Using directional antenna restricts the direction of signal propagation through air. This is one of the crude ways of limiting packet dispersion.

HELLO Flood Attack

The attacker node floods the network with a high-quality route with a powerful transmitter. So, every node can forward their packets towards this node hoping it to be a better route to destination. Some can forward packets for those destinations which are out of the reach of the attacker node. A single high-power transmitter can convince that all the nodes are his neighbor. The attacker node need not generate a legitimate traffic; it can just perform a selective replay attack as its power overwhelms other transceivers.

Bogus Registration Attack

A Bogus registration attack is an active attack in which an attacker disguises itself as another node either by sending stolen beacon or generating such false beacons to register himself with a node as a neighbor. Once registered, it can snoop transmitted packets or may disrupt the network altogether. But this type of attack is difficult to achieve as the attacker needs to intimately know the masquerading node's identity and network topology. Encrypting packets before sending and secure authentication in route discovery (SRDP, SND, SNRP, ARAN, etc) will limit the severity of attack to some extent as attacker node has no previous knowledge of encryption method.

Man in Middle Attack

In Man in Middle attack, the attacker node creeps into a valid route and tries to sniff packets flowing through it. To perform man in middle attack, the attacker first needs to be part of that route. It can do that by either temporarily disrupting the route by deregistering a node by sending malicious disassociation beacon captured previously or registering itself in next route timeout event. One way of protecting packets flowing through MANET from prying eyes is encrypting each packet. Though key distribution becomes a security issue.

Rushing Attack

In AODV or related protocol, each node before transmitting its data, first establishes a valid route to destination. Sender node broadcasts a RREQ (route request) message in neighborhood and valid routes replies with RREP (route reply) with proper route information. Some of the protocols use duplicate suppression mechanism to limit the route request and reply chatter in the network. Rushing attack exploits this duplicate suppression mechanism. Rushing attacker quickly forwards with a malicious RREP on behalf of some other node skipping any proper processing. Due to duplicate suppression, actual valid RREP message from valid node will be discarded and consequently the attacking node becomes part of the route. In rushing attack, attacker node does send packets to proper node after its own filtering is done, so from outside the network behaves normally as if nothing happened. But it might increase the delay in packet delivering to destination node.

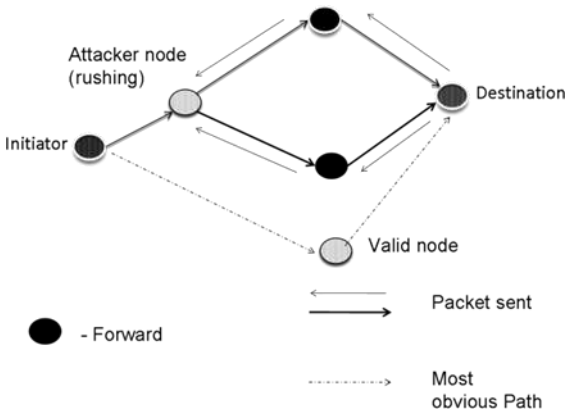


Figure 6: Rushing Attack

Few of the protocols that might help in resolving Rushing attack:

- **SEDYMO:** Secured Dynamic MANET On-Demand is similar to DYMO but it dictates intermediate node must add routing information while broadcasting the routing messages and no intermediate node should delete any routing information from previous sender while broadcasting. It also incorporates hash chains and digital signature to protect the identity.

- **SRDP [23]:** Secure Route Discovery Protocol is security enhanced Dynamic Source routing (DSR) protocol.
- **SND [26]:** Secure Neighbor Detection is another method of verifying each neighbor's identity within a maximum transmission range.

Cache Poisoning Attack

Generally, in AODV, each node keeps few of its most recent transmission routes until timeout occurs for each entry. So, each route lingers for some time in node's memory. If some malicious node performs a routing attack, then they will stay in node's route table until timeout occurs or a better route is found. An attacker node can advertise a zero metric to all of its destinations. Such route will not be overwritten unless timeout occurs. It can even advertise itself as a route to a distant node which is out of its reach. Once it becomes a part of the route, the attacker node can perform its malicious activity. Effect of Cache poisoning can be limited by either adding boundary leashes or by token authentication. Also, each node can maintain its friend-foe list based on historical statistics of neighboring nodes performance.

Few of the Mitigation Methods Proposed

- **SAODV [29]:** Secure AODV is an extension to AODV protocol that adds each node to exchange signed routing messages. Each node has its own public key which it uses to sign routing messages. Also, SAODV uses hop count as a metric for shortest-route as AODV and uses hash chains to secure hop count information in route messages.
- **ARAN [16][18][28]:** Authenticated Routing protocol for Ad-hoc Networks uses similar techniques as SAODV. ARAN uses certificates issued by a third-party certification authority.
- **SNRP [16]:** Secure Neighbor Routing protocol uses security enhanced Neighbor Lookup Protocol (NLP) to secure MANET routing. Newly added node uses public key to participate in MANET.

Blackmailing and Co-operative Blackmailing Attack

In a blackmailing attack or more effectively co-operative blackmailing attack, attacker nodes accuse an innocent node as harmful node. This attack can effectively be done on those distributed protocols that establish a good and bad node list based on review of participating nodes in MANET. Few of the protocols tries to make them more secure by using majority voting principle, but still if sufficient no. of attacker nodes becomes part of the MANET it can bypass that security also.

Another generic method of this attack will be, sending invalid RREP messages with advertising an unnecessarily high cost to certain nodes.

Known Mitigation Techniques

- **Dynamic Trust Based, Distributed IDs [22]:** As MANET routing is a co-operative process; while building a route each node must evaluate its neighbor nodes. This method builds a distributed trust relationship and maintains dynamic trust information. As the trust is part of a long chain, single malicious node cannot victimize an innocent node easily.
- **Friend List Based [22]:** Another solution will be building a friend list of trusted nodes. Node's identity must be determined by the user who created the MANET. So, it becomes a closed system of trusted node

Sybil Attack

Sybil attack manifests itself by faking multiple identities by pretending to be consisting of multiple nodes in the network. So one single node can assume the role of multiple nodes and can monitor or hamper multiple nodes at a time. If Sybil attack is performed over a blackmailing attack, then level of disruption can be quite high. Success in Sybil attack depends on how the identities are generated in the syste

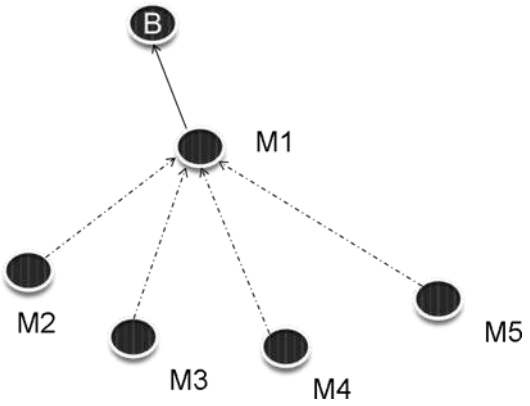


Figure 7: Sybil Attack

In figure 7, node M1 assumes identities of M2, M3, M4, and M5. So, to node B, M1 is equivalent to those nodes One way of mitigating this attack is maintaining a chain of trust, so single identity is generated by a hierarchical structure which may be hard to fake.

Characteristics of Mobile Ad-Hoc Networks

In MANET, each mobile node acts both as a host and router. That is, it is autonomous in behavior. The main characteristics which MANETs have to achieve are self-configuration, peer-to-peer connection among hosts and dynamic multi-hop routing. Some basic characteristics are:

- **Multi-hop Routing:** When a source node and destination node is out of radio range, MANET finds out various paths through intermediate nodes which are in direct range of network, this is multi-hop routing process.
- **Distributed Operation:** There is no centralized firewall for overall security, routing and host configuration. There is infrastructure less topology.
- Topological dynamism: The topology of this network is dynamic in nature. The nodes can join or detach from the network anytime due to mobility and frequent node failure.
- **Fluctuating Link Bandwidth:** There is effect of high bit error rate common in wireless communication.
- **Limited Energy Resources:** Mobile nodes have less power, memory and weightless features. Wireless devices are battery operated thus, designing mechanisms used to reduce energy consumption are: (a) devices go into sleep state when idle (b) routing paths that reduce energy consumption, (c) improve communication and data delivery structures to minimize energy consumption and (d) reduce overhead due to networking.

Applications of Mobile Ad-Hoc Networks

The Ad-hoc system is intended to be utilized where it is not dependably reachable. Its primary qualities are consistent connectivity with nodes in the network area and the way that the system comprises of taking an interested node. Several applications of Ad-hoc network are discussed below:

- **Rescue Operations:** There are different circumstances when there is no infrastructure present, therefore it is important to build up a communication system. In situations like natural disaster, wars and emergency in immature nations, specially appointed systems i.e. Ad hoc networks can convey rapidly and have no need of any framework.
- **Home Networks:** Today, numerous family units have PCs in various rooms. People might want to connect these PCs to each other and transfer files so they do this by creating an Ad hoc network between them.
- **Educational Applications:** Ad-hoc networks are used to setup virtual class & conference rooms.
- **Games:** This is an example of a completely commercial aspect of the Ad-hoc networks. People can play with the general population inside the network area. This is an awesome approach of interest in broad daylight zones as in trains, train stations or air terminals.
- **Military Operations:** Mobile Ad hoc networks are used in unmanned army system for surveillance and future combat operations. This has demanded the development of state-of-the-art MANET solutions for the reliability, security and scalability needs of the defense communications environment. It was the

U.S Department of Defense that supported the principal exploration of specially employed systems to empower parcel

Challenges in Mobile Ad-Hoc Networks

There are several issues in Ad-hoc networks which make them very complex to integrate with the existing global network. The Mobile Ad-hoc Network (MANET) has become an important communication technology in the areas like military defense networks, rescue operations command centers, vehicular networks, etc. [TRI 2016]. Generally, the most prominent problems are the identification of mobile terminals and the correct routing of mobile packets between each terminal.
The problems are discussed below:

- **Routing:** Routing is a most notable issue in wireless networks specially in systems having a consistent network of different nodes in its neighborhood. In this every node behaves as a switch and advances each other‟s data packages to enable data sharing between portable nodes.
- **Security:** A wireless link is much more vulnerable to attacks than a wired link. The user can insert spurious information into routing packets and cause routing loops, longtime- outstand advertisements of false or old routing table updates. Security has several unsolved issues that are needed to be solved to make the Ad-hoc networks a good solution.
- **Quality of Service:** QoS is a problematic job for the engineers, because of the fact that the topology of a specially appointed system will always show some signs of change in topology. Saving assets and maintaining a specific nature of administration, while the system condition continually changes, is exceptionally tedious [PER 2003].
- **Load Balancing:** A load balancing strategy distributes MANET-Internet traffic between existing gateways, thus avoiding heavily loaded gateways where there are less loaded ones. The load balancing mechanism is applied at various points, e.g., during gateway discovery or gateway selection [MOJ 2020].
- **Power Control:** Power control is one of the main objectives in specially appointed ad hoc system. Since each cell phone utilizes battery for force supply, yet it is for a short-term period. Power consumption in cell phones count on upon various sort of directing conventions or steering strategies.

Conclusion

We have tried to categorize the different types of ad hoc security attacks solely based on their characteristics to considerably reduce the mitigation period. By bringing the attacks under these two broad categories the complicacy of naming also reduces. We have also kept a close look on the existing algorithms needed to mitigate the attacks and have tried to bind the attacks into categories according to that, some attacks have characteristics which makes them unsuitable to be

categorized into these categories, so they have been kept away from this topic of discussion for the time being. Further study is in progress to find out more common characteristics of the attacks to more strongly bind them into these categories and to ably design more powerful algorithm in mitigating DATA and CONTROL traffic attacks.

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Emerging Non-Pharmaceutical and Nanotechnology-Based Drug Delivery Approaches

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Abstract

Non-pharmaceutical and nano-drug delivery systems represent frontier technologies in targeted therapeutics, controlled release, and biocompatible medical applications. These systems leverage advances in materials science, nanotechnology, and biomedical engineering to transport therapeutic agents while reducing toxicity, improving bioavailability, and overcoming biological barriers. This chapter provides a comprehensive discussion of non-pharmaceutical approaches (physical, mechanical, and biologically-derived delivery systems), nano-based delivery platforms (liposomes, polymeric nanoparticles, dendrimers, inorganic nanoparticles), mechanisms of drug release, targeting strategies, clinical applications, regulatory considerations, challenges, and future trends. Integration of multidisciplinary technologies underscores the translational potential from bench to bedside.

Keywords: Non-pharmaceutical delivery, Nano-drug delivery, Controlled release, Targeted therapy, Liposomes, Polymeric nanoparticles, Dendrimers, Biocompatibility

Introduction

The efficient and site-specific delivery of therapeutic agents to diseased tissues or target cells continues to represent one of the most critical and persistent challenges in modern medicine. Conventional drug delivery approaches, including oral, parenteral, and topical dosage forms, frequently exhibit inherent limitations such as poor aqueous solubility of drug molecules, low and variable bioavailability, rapid systemic clearance, extensive first-pass metabolism, and non-selective biodistribution. As a consequence, only a small fraction of the administered dose often reaches the intended biological target, while the remaining portion distributes to healthy tissues, leading to dose-dependent systemic toxicity and adverse side effects. These drawbacks are particularly pronounced in the treatment of chronic and life-threatening diseases such as cancer, neurological disorders, inflammatory conditions, and genetic diseases, where prolonged therapy and high drug concentrations are usually required. In response to these challenges, considerable scientific attention has been directed toward the development of advanced delivery platforms capable of improving therapeutic performance by protecting drug molecules from premature degradation, controlling their release rate, prolonging circulation time, and enhancing accumulation at the site of action. The emergence of non-pharmaceutical delivery technologies and nano-drug carrier systems represents a paradigm shift in drug delivery research, as these approaches focus not only on the chemical nature of the drug but also on the engineering of delivery devices and carriers that can actively modulate drug transport, distribution, and cellular uptake (Kumar et al., 2020).

Non-pharmaceutical delivery systems primarily rely on physical, mechanical, and biologically inspired strategies to facilitate drug transport across biological barriers that normally restrict the entry of therapeutic agents. These approaches include minimally invasive techniques such as microneedle-based transdermal systems, electroporation-assisted membrane permeabilization, ultrasound-mediated transport, and other energy-driven methods that transiently disrupt tissue or cellular barriers to enhance drug penetration. In addition to these physical strategies, biologically derived delivery platforms such as cell-based carriers and naturally occurring vesicular systems have gained significant attention because of their intrinsic biocompatibility and ability to interact efficiently with physiological transport pathways. Such systems are particularly valuable for delivering macromolecules, nucleic acids, proteins, and vaccines, which are otherwise difficult to administer using traditional dosage forms. By bypassing conventional oral and injectable routes and by reducing dependence on high systemic drug exposure, non-pharmaceutical delivery technologies offer new possibilities for localized, controlled, and patient-friendly therapeutic interventions.

Parallel to these developments, nano-drug delivery systems have emerged as one of the most powerful tools for improving pharmacokinetic behavior and therapeutic

selectivity. In these systems, drug molecules are either encapsulated within or conjugated to nanoscale carriers, typically in the size range of approximately 1–100 nm, enabling precise control over drug solubility, stability, and release characteristics. The nanoscale dimensions of these carriers allow them to interact efficiently with biological structures such as cell membranes, intracellular organelles, and vascular endothelium, thereby facilitating enhanced cellular uptake and improved tissue penetration. Furthermore, nano-carriers can be engineered with surface modifications, stealth coatings, and targeting ligands to prolong systemic circulation and promote selective recognition of disease-specific receptors. As a result, nano-drug delivery platforms are capable of significantly improving drug accumulation at pathological sites while minimizing off-target exposure (Singh & Nalwa, 2019). This chapter therefore presents a comprehensive and systematic discussion of the fundamental principles, classification, design strategies, transport mechanisms, and biomedical applications of non-pharmaceutical and nano-drug delivery systems, highlighting their growing importance in modern therapeutic development and their potential to transform future clinical practice.

Non-Pharmaceutical Delivery Systems

Scope of Non-Pharmaceutical Delivery Systems

Non-pharmaceutical delivery refers to physical or biologically-based methods of transporting therapeutic agents without relying solely on chemical excipients or systemic administration. These methods often enhance delivery efficiency, reduce invasiveness, and improve patient compliance (Patel et al., 2021).

Physical Methods

Microneedle Arrays

Microneedle arrays are micron-sized needle structures designed to penetrate the stratum corneum in a minimally invasive and almost painless manner, thereby enabling efficient transdermal delivery of therapeutic agents. As shown in Figure 1, the microneedles create uniform microchannels in the upper layers of the skin without reaching deeper pain-sensitive tissues, which allows drugs to diffuse directly into the viable epidermis and superficial dermis. This mechanism significantly improves the delivery of poorly permeable molecules such as peptides, vaccines and nano-carriers, while enhancing patient compliance and reducing the need for conventional injections (Prausnitz & Langer, 2008).

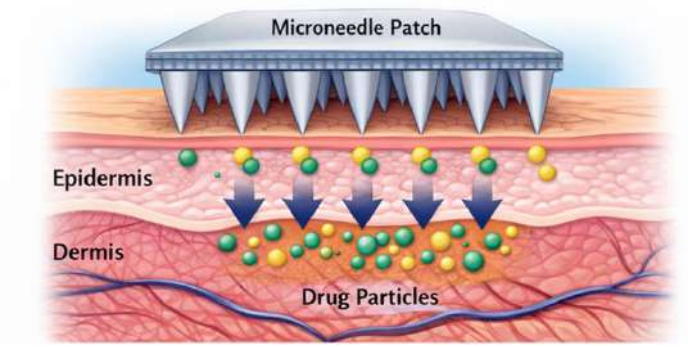

Figure 1. Schematic of a microneedle array penetrating the skin to deliver therapeutic agents.

Electroporation

Electroporation is a physical, non-pharmaceutical delivery technique in which brief and precisely controlled electrical pulses are applied to cells or tissues to temporarily increase the permeability of the cell membrane. The externally applied electric field induces a rapid rearrangement of lipid molecules within the plasma membrane, resulting in the formation of transient and reversible nanoscale pores. These short-lived pores allow therapeutic agents that normally cannot cross the lipid bilayer—such as hydrophilic drugs, proteins, plasmid DNA and small interfering RNA—to enter the intracellular environment directly.

The pores reseal naturally once the electric pulses are discontinued, thereby restoring membrane integrity and minimizing permanent cellular damage. Owing to this reversible permeabilization mechanism, electroporation significantly enhances intracellular delivery efficiency while avoiding the need for viral vectors or chemical permeation enhancers, making it especially useful for localized gene therapy and targeted cancer treatment (Neumann et al., 2017).

Ultrasound-Mediated Delivery

Ultrasound-mediated drug delivery is a non-pharmaceutical, externally triggered technique in which acoustic energy is used to enhance the transport of therapeutic agents across biological barriers and cellular membranes. When ultrasound waves are applied to tissues, they generate mechanical oscillations that produce localized pressure variations in the surrounding medium. These oscillations can induce acoustic cavitation, in which microscopic gas bubbles repeatedly expand and collapse, generating localized mechanical stress and fluid movement known as acoustic streaming. As a result, the structural organization of cell membranes and intercellular junctions is temporarily disturbed, leading to a reversible increase in membrane permeability and improved penetration of drug molecules into tissues.

In many therapeutic applications, ultrasound is combined with intravenously or locally administered microbubbles to further amplify the delivery effect. The

interaction between ultrasound waves and microbubbles produces strong mechanical forces near cell surfaces, which enhances pore formation in the plasma membrane and promotes rapid intracellular entry of drugs, proteins, and nucleic acids. Importantly, once the ultrasound exposure is stopped, membrane integrity is gradually restored, allowing the technique to remain largely non-destructive when appropriately controlled. The feasibility and therapeutic relevance of this approach have been widely demonstrated in experimental and translational studies, including the work reported by Ghaleb A. Husseini and William G. Pitt, who highlighted the strong potential of ultrasound-assisted systems for improving localized drug transport.

Ultrasound-mediated delivery has shown particular promise in brain drug delivery, where it can be used to transiently and safely enhance permeability of the blood–brain barrier, allowing otherwise impermeable therapeutic agents to reach the central nervous system. In oncology, the technique is increasingly explored for chemotherapy enhancement, as ultrasound-induced permeabilization and microbubble activity significantly increase drug accumulation within tumor tissues, leading to improved therapeutic efficacy while reducing systemic exposure and adverse effects (Husseini & Pitt, 2009).

Biological Carriers

Cell-Mediated Delivery

Cell-mediated delivery is an emerging non-pharmaceutical strategy in which living cells such as red blood cells, leukocytes and stem cells are employed as active carriers to transport therapeutic agents to diseased tissues. In this approach, drugs or nano-formulations are either encapsulated within the carrier cells or attached to their surface, allowing the cells to exploit their natural homing and trafficking abilities within the body. After systemic administration, these carrier cells migrate through the circulation and preferentially accumulate at sites of inflammation, injury or tumor growth, where the therapeutic payload is subsequently released. This biologically driven transport mechanism provides superior biocompatibility, prolonged circulation time and reduced premature drug clearance when compared with synthetic carriers alone. Among various immune cells, macrophages are particularly attractive because of their strong chemotactic migration toward tumor microenvironments and hypoxic regions. Experimental studies, including those reported by Vladimir R. Muzykantov and co-workers (Cheng et al., 2015), have demonstrated that macrophage-based delivery systems significantly enhance tumor targeting efficiency and intracellular drug accumulation, thereby improving therapeutic outcomes while minimizing off-target toxicity.

Extracellular Vehicles (EVs)

Extracellular vehicles (EVs), including exosomes, are naturally secreted nanosized vesicles that play a key role in intercellular communication by transferring biomolecules such as proteins, lipids and nucleic acids between cells. As illustrated in Figure 2, EVs possess a lipid bilayer structure that effectively protects sensitive cargo such as miRNA from enzymatic degradation and facilitates direct fusion or endocytic uptake by target cells. Owing to their endogenous origin, EVs exhibit excellent biocompatibility and very low immunogenicity, making them highly attractive carriers for therapeutic delivery. However, major challenges remain in achieving standardized isolation methods and scalable, reproducible production for clinical translation.

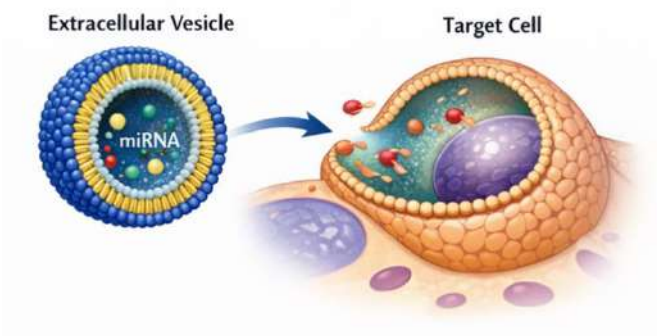

Figure 2. Extracellular vesicle encapsulating miRNA delivered to a target cell.

Nano-Drug Delivery Systems

Overview

Nano-drug delivery utilizes engineered nanoscale carriers to enhance drug solubility, protect therapeutic agents from enzymatic and chemical degradation, and improve stability in biological environments. These systems enable controlled and site-specific delivery of drugs to diseased tissues, thereby increasing therapeutic efficacy, reducing systemic toxicity and improving overall pharmacokinetic performance of modern pharmaceutical formulations.

Liposomal Systems

Liposomal drug delivery systems are spherical vesicles composed of one or more lipid bilayers surrounding an aqueous core, enabling the simultaneous incorporation of hydrophilic and hydrophobic therapeutic agents. Hydrophilic drugs are entrapped within the internal aqueous compartment, while hydrophobic drugs are incorporated into the lipid bilayer and are released mainly through fusion or interaction with cellular membranes (Figure 3). Liposomes are biocompatible, scalable and significantly reduce systemic toxicity. A well-known clinical example is liposomal

doxorubicin (Doxil), reported by Yechezkel Barenholz (2012) for cancer therapy (Barenholz, 2012).

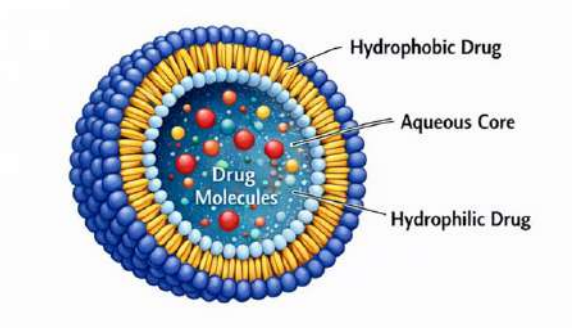

Figure 3: Liposomal Drug Delivery System

Polymeric Nanoparticles

Polymeric nanoparticles are nanocarriers formed from biodegradable and biocompatible polymers such as poly (lactic-co-glycolic acid) (PLGA), widely used for controlled drug delivery applications. Drug release from these systems mainly occurs through diffusion of the entrapped drug across the polymer matrix and by gradual polymer degradation within the physiological environment. A major advantage of polymeric nanoparticles is the ability to precisely tune release profiles and degradation rates by modifying polymer composition and molecular weight, making them highly suitable for sustained-release vaccines and long-acting antibiotic formulations (Danhier et al., 2012).

Dendrimers

Dendrimers are highly branched, tree-like polymeric nanostructures with a precisely controlled and symmetrical architecture. Their surface contains a large number of functional groups that enable efficient drug conjugation, targeting ligand attachment and imaging probe loading, while their uniform size and shape ensure predictable biological behavior. Owing to these features, dendrimers are widely explored for gene delivery and as contrast agents in diagnostic imaging (Astruc et al., 2010).

Inorganic Nanoparticles

Inorganic nanoparticles such as gold, silica and magnetic nanoparticles are widely investigated as advanced nano-drug carriers because of their distinctive optical, electronic and magnetic properties. These unique characteristics enable their dual use in therapy and diagnosis, commonly referred to as theranostics. Major biomedical applications include photothermal therapy using gold nanoparticles and magnetic resonance imaging contrast enhancement using magnetic nanoparticle systems (Huang et al., 2011).

Targeting Strategies

Passive Targeting

Exploits physiological features, e.g., Enhanced Permeability and Retention (EPR) effect in tumors.

Active Targeting

Passive targeting exploits physiological abnormalities of diseased tissues, particularly the enhanced permeability and retention (EPR) effect in tumors, which allows nanocarriers to accumulate preferentially at the pathological site. In contrast, active targeting involves surface functionalization of nanocarriers with ligands such as antibodies or peptides to enable receptor-mediated cellular uptake and improved site-specific drug delivery, as illustrated in Figure 4.

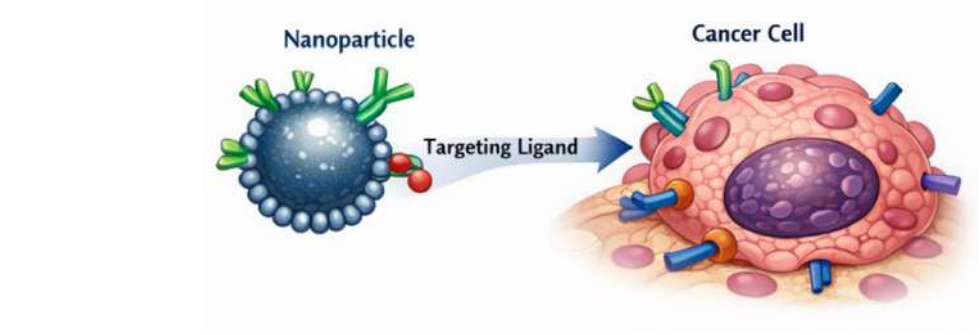

Figure 4. Nano-carrier with targeting ligand binding to cell surface receptors.

Pharmacokinetics and Biodistribution

Nano-drug delivery systems significantly modify the pharmacokinetic and biodistribution behavior of therapeutics by altering their absorption, distribution, metabolism and excretion (ADME) profiles. Owing to their nanoscale size, particularly above 5 nm, these carriers exhibit reduced renal clearance and prolonged circulation time. In addition, surface modification such as PEGylation helps minimize macrophage uptake, thereby improving systemic stability and target-site accumulation.

Clinical Applications

Nano-carriers have demonstrated significant benefits in cancer therapy by enhancing the selective accumulation of chemotherapeutic agents in tumor tissues, thereby improving treatment efficacy while markedly reducing systemic toxicity and adverse effects (Peer et al., 2007). In gene therapy, non-viral delivery systems, particularly polymeric nanoparticles, are widely employed for the safe and efficient transport of siRNA and plasmid DNA, offering improved stability and cellular uptake. For neurological applications, effective drug delivery remains challenging because of the restrictive blood–brain barrier; however, ligand-modified

nanocarriers have shown promising potential for targeted transport to brain tissues (Zhong & Auguste, 2010).

Regulatory and Safety Considerations

Regulatory and safety considerations play a crucial role in the clinical translation of nano-drug delivery systems. From a safety perspective, nanotoxicology studies have highlighted potential risks such as oxidative stress, inflammatory responses, unintended interactions with biological components and long-term accumulation of non-biodegradable nanomaterials in vital organs. At the regulatory level, dedicated frameworks for nanomedicines are still evolving, and regulatory authorities increasingly require comprehensive physicochemical characterization, standardized manufacturing protocols, reproducible quality control, and detailed preclinical safety evaluation to ensure product consistency, reliability and patient safety.

Challenges and Future Directions

The large-scale translation of non-pharmaceutical and nano-drug delivery systems faces several practical challenges, particularly in manufacturing scale-up, where batch-to-batch reproducibility, process complexity and high production costs remain major limitations. Maintaining consistent particle size, surface characteristics and drug loading during industrial production is essential for regulatory approval. Future developments are expected to focus on personalized medicine, in which nano-delivery platforms will be integrated with patient-specific diagnostic and molecular data to design tailored and more effective therapeutic strategies.

Conclusion

Non-pharmaceutical and nano-drug delivery systems represent a transformative advancement in modern therapeutics by enabling precise, controlled and site-specific delivery of drugs, genes and biological molecules. These technologies significantly enhance therapeutic efficacy while minimizing systemic exposure and adverse effects, thereby improving patient safety and treatment outcomes. By integrating physical delivery techniques, biologically derived carriers and engineered nanocarriers, it is now possible to overcome major biological barriers and address limitations associated with conventional dosage forms. Continued multidisciplinary research involving pharmaceutical sciences, materials engineering, biotechnology and clinical medicine, together with harmonized regulatory frameworks, will be essential for accelerating the large-scale translation of these innovative delivery platforms into routine clinical practice.

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Recombinant Therapeutics and Biotechnology in Diabetes Treatment

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Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from impaired insulin secretion, insulin action, or both. The global prevalence of diabetes has increased significantly, creating an urgent need for effective and safe therapeutic strategies. Biotechnology has played a major role in transforming diabetes management, particularly through the development of recombinant therapeutics such as human insulin, insulin analogues, and recombinant proteins that improve glycemic control. Recombinant DNA technology, protein engineering, gene therapy, and stem cell research have contributed to advances in diabetes treatment by improving drug efficacy, safety, and delivery. Modern biotechnological approaches also focus on developing long-acting insulin, glucose-responsive insulin systems, and regenerative therapies aimed at restoring pancreatic β-cell function. This chapter discusses the role of recombinant therapeutics and biotechnology in diabetes treatment, highlighting recent developments and future prospects in this rapidly evolving field.

Keywords: Recombinant insulin, Diabetes biotechnology, Protein engineering, Gene therapy

Introduction

Diabetes mellitus is one of the most common non-communicable diseases affecting millions of people worldwide. It is broadly classified into Type 1 diabetes, which results from autoimmune destruction of pancreatic β-cells, and Type 2 diabetes, which is associated with insulin resistance and impaired insulin secretion. Long-term complications of diabetes include cardiovascular disease, neuropathy, nephropathy, and retinopathy, which significantly reduce quality of life.

Traditional treatment strategies relied on insulin extracted from animal pancreas, which often caused allergic reactions and variability in therapeutic response. The advent of biotechnology, particularly recombinant DNA technology, revolutionized diabetes treatment by enabling the production of human insulin identical to the natural hormone. Since then, advances in genetic engineering, protein modification, and drug delivery systems have significantly improved therapeutic options for diabetic patients. Biotechnology continues to provide innovative solutions aimed at improving glycemic control and preventing complications.

Recombinant DNA Technology and the Production of Human Insulin

The production of recombinant human insulin marked one of the earliest and most successful applications of biotechnology in medicine. Recombinant DNA technology involves inserting the human insulin gene into microbial hosts such as Escherichia coli or yeast, which then produce insulin in large quantities under controlled fermentation conditions. This approach ensures high purity, consistency, and safety compared to animal-derived insulin.

The availability of recombinant insulin has greatly improved diabetes management by reducing immunogenic reactions and enabling large-scale production to meet global demand. Continuous improvements in expression systems and purification techniques have enhanced yield and reduced production costs, making recombinant insulin widely accessible.

Insulin Analogues and Protein Engineering

Protein engineering has enabled the development of insulin analogues with modified amino acid sequences to improve pharmacokinetic properties. Rapid-acting insulin analogues are designed to act quickly after administration, while long-acting analogues provide sustained glucose control over extended periods. These modifications help mimic physiological insulin secretion more closely and reduce the risk of hypoglycemia.

Advances in structural biology and computational modeling have facilitated the design of insulin molecules with improved stability, solubility, and absorption. Such

innovations have significantly enhanced patient compliance and therapeutic effectiveness.

Recombinant Therapeutic Proteins in Diabetes Management

In addition to insulin, several recombinant proteins are used in diabetes treatment. Glucagon-like peptide-1 (GLP-1) receptor agonists and other peptide-based therapeutics improve insulin secretion and reduce blood glucose levels. These biologics are produced using recombinant DNA technology and offer advantages such as longer half-life and improved metabolic control.

Recombinant enzymes and growth factors are also being explored for preventing diabetic complications by promoting tissue repair and improving metabolic functions. These therapeutic proteins represent an expanding area of pharmaceutical biotechnology.

Gene Therapy and Regenerative Approaches

Gene therapy is an emerging approach aimed at correcting genetic or functional defects associated with diabetes. Strategies include delivering genes that enhance insulin production, improve glucose metabolism, or protect pancreatic β-cells from autoimmune destruction. Viral and non-viral vectors are being studied for efficient gene delivery to target tissues.

Regenerative medicine, including stem cell therapy, offers the possibility of restoring insulin-producing cells in diabetic patients. Researchers are exploring the differentiation of stem cells into functional β-cells and their transplantation to restore endogenous insulin production. Although still under investigation, these approaches hold significant promise for long-term diabetes management.

Nanobiotechnology and Drug Delivery Systems

Nanobiotechnology has contributed to the development of advanced drug delivery systems for diabetes treatment. Nanoparticles, liposomes, and polymer-based carriers improve insulin stability and enable controlled release, reducing the frequency of injections. Research is also focused on developing oral insulin formulations and glucose-responsive insulin systems that release insulin in response to blood glucose levels.

Such technologies aim to improve patient comfort and adherence to treatment while maintaining effective glycemic control. The integration of biosensors and smart drug delivery devices is expected to further enhance diabetes management in the future.

Future Prospects in Diabetes Biotechnology

Rapid advances in genome editing, personalized medicine, and artificial pancreas systems are expected to transform diabetes treatment. Continuous glucose monitoring combined with automated insulin delivery is already improving patient

outcomes. Genome editing tools such as CRISPR are being investigated for modifying genes involved in insulin regulation and glucose metabolism.

The integration of biotechnology with digital health technologies, including wearable biosensors and telemedicine, is expected to improve early diagnosis and personalized treatment strategies. Continued research and clinical trials will be essential to translate these innovations into widely accessible therapies.

Conclusion

Biotechnology has revolutionized the treatment of diabetes through the development of recombinant insulin, engineered insulin analogues, therapeutic proteins, and advanced drug delivery systems. Emerging approaches such as gene therapy, stem cell research, and nanobiotechnology offer promising solutions for long-term disease management and potential cures. As research continues to advance, biotechnological innovations will play an increasingly important role in improving the quality of life of diabetic patients and reducing the global burden of this chronic disease.

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Quality by Design (QbD) and Quality Risk Management

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Abstract

Quality by Design (QbD) and Quality Risk Management (QRM) are modern scientific approaches that ensure pharmaceutical products are consistently safe, effective, and of high quality. Unlike traditional quality control methods that rely mainly on end-product testing, QbD emphasizes building quality into the product during development by understanding formulation and process variables. QRM complements QbD by systematically identifying, evaluating, and controlling risks that may affect product quality throughout the lifecycle. Regulatory authorities such as the International Council for Harmonisation (ICH) strongly advocate these approaches through guidelines including ICH Q8, Q9, and Q10. This review article discusses the principles, elements, tools, regulatory framework, applications, advantages, challenges, and future perspectives of QbD and risk management in pharmaceutical development and manufacturing.

Keywords: Quality by Design (QbD); Quality Risk Management (QRM); Pharmaceutical Quality; ICH Q8, Q9, Q10; Critical Quality Attributes (CQAs); Critical Process Parameters (CPPs). Process Analytical Technology (PAT); Design Space; Risk Assessment; Regulatory Framework; Pharmaceutical Development; Manufacturing Control. Product Lifecycle Management; Risk-Based Approach; Continuous Improvement; Patient Safety; Drug Product Quality.

Introduction

The pharmaceutical industry plays a critical role in protecting public health by ensuring that medicines are safe, effective, and of consistent quality. Traditionally, quality assurance relied heavily on testing finished products to verify compliance

with predefined specifications. However, this reactive approach often failed to detect problems arising from variability in raw materials, manufacturing processes, or environmental conditions. As a result, product recalls, batch failures, and inconsistent therapeutic performance were common concerns. To address these issues, the concept of Quality by Design (QbD) was introduced as a proactive, science- and risk-based approach to pharmaceutical development. QbD focuses on designing quality into the product from the beginning rather than relying solely on end-product testing. It emphasizes understanding the relationship between formulation components, manufacturing processes, and product performance. Quality Risk Management (QRM) complements QbD by providing structured tools to identify, assess, and control potential risks to product quality. Together, QbD and QRM represent a paradigm shift toward lifecycle-based quality assurance.

Regulatory Framework

- **ICH Q8 - Pharmaceutical Development**

ICH Q8 provides guidance on applying QbD principles during pharmaceutical development. It encourages a systematic approach that includes defining the Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), and establishing a design space. The guideline promotes scientific understanding of how formulation and process variables affect product quality.

- **ICH Q9 - Quality Risk Management**

ICH Q9 outlines principles and tools for risk management applicable throughout the product lifecycle. It defines risk as the combination of the probability of harm and the severity of that harm. The guideline provides structured methods for risk assessment, control, communication, and review.

- **ICH Q10 - Pharmaceutical Quality System**

ICH Q10 describes a comprehensive quality system that integrates QbD and QRM principles. It emphasizes continuous improvement, lifecycle management, and management responsibility in maintaining product quality.

Concept of Quality by Design

Quality by Design is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management. The core idea is that quality cannot be tested into a product; it must be built into it. QbD involves identifying factors that influence product quality and controlling them to ensure consistent performance. It requires thorough knowledge of raw materials, manufacturing processes, equipment, and environmental conditions. By understanding these variables, manufacturers can design robust processes capable of producing products that meet specifications consistently.

Key Elements of QbD

- **Quality Target Product Profile (QTPP)**

The QTPP describes the intended characteristics of the final product, including dosage form, route of administration, strength, pharmacokinetics, stability, and therapeutic performance. It serves as the foundation for development activities.

- **Critical Quality Attributes (CQAs)**

CQAs are measurable properties that must be controlled to ensure product quality. Examples include drug potency, dissolution rate, particle size, sterility, and impurity levels.

- **Critical Material Attributes (CMAs)**

CMAs refer to the physical, chemical, or biological properties of raw materials that influence CQAs. For example, the particle size of an active pharmaceutical ingredient can affect dissolution rate and bioavailability.

- **Critical Process Parameters (CPPs)**

CPPs are process variables that have a significant impact on CQAs. Examples include mixing time, granulation moisture content, drying temperature, compression force, and coating conditions.

- **Design Space**

The design space is the multidimensional combination of CMAs and CPPs that ensures product quality. Operating within this space provides flexibility while maintaining compliance.

- **Control Strategy**

A control strategy includes planned controls for materials, process parameters, equipment, and testing to ensure consistent production within the design space.

Design of Experiments (DoE)

Design of Experiments is a statistical tool used in QbD to study the effects of multiple variables simultaneously. It helps identify critical factors, interactions between variables, and optimal process conditions. DoE reduces the number of experiments required compared to traditional one-factor-at-a-time approaches and provides a scientific basis for establishing the design space.

Process Analytical Technology (PAT)

Process Analytical Technology involves real-time monitoring and control of manufacturing processes using advanced analytical tools. PAT enables continuous assessment of CPPs and CQAs during production, allowing immediate adjustments to maintain quality. Techniques such as near-infrared spectroscopy, Raman spectroscopy, and online sensors are commonly used in PAT systems.

Step No.	QbD Element	Description	Purpose in Development
1	Quality Target Product Profile (QTPP)	Defines desired characteristics of the final product (dosage form, route, strength, stability)	Serves as the foundation for product development
2	Critical Quality Attributes (CQAs)	Physical, chemical, biological properties that must be controlled	Ensures product safety, efficacy, and quality
3	Critical Material Attributes (CMAs)	Properties of raw materials that influence CQAs	Helps select suitable materials and suppliers
4	Critical Process Parameters (CPPs)	Process variables that impact CQAs	Ensures consistent manufacturing performance
5	Risk Assessment	Evaluation of how CMAs and CPPs affect CQAs	Identifies high-risk factors requiring control
6	Design of Experiments (DoE)	Statistical method to study variable interactions	Optimizes formulation and process condition
7	Design Space	Range of operating conditions that assure quality	Provides flexibility while maintaining compliance

Flow chart: 1 Elements of QbD

Quality Risk Management (QRM)

Provides flexibility while maintaining compliance Quality Risk Management (QRM) is a systematic, science-based approach used in the pharmaceutical industry to ensure that risks to product quality and patient safety are identified, assessed, controlled, and continuously monitored throughout the product lifecycle. It is strongly recommended by the ICH Q9 guideline and forms a core component of Quality by Design (QbD). The main objective of QRM is to make informed decisions based on scientific evidence and the potential impact of risks on patients, rather than relying on assumptions. Risks in pharmaceuticals may arise from raw materials, manufacturing processes, equipment, personnel, environment, storage, or distribution. A well-implemented QRM system improves product reliability, regulatory compliance, and overall process efficiency while minimizing failures, recalls, and harm to patients.

Risk Identification

Risk identification is the first step in QRM and involves systematically recognizing potential hazards that could negatively affect product quality, safety, or efficacy. A hazard is any source of potential harm. In pharmaceutical manufacturing, hazards can originate from many sources, including contaminated raw materials, malfunctioning equipment, inadequate cleaning procedures, operator errors, environmental factors such as temperature and humidity fluctuations, and improper storage conditions. Historical data, deviation reports, customer complaints, audit findings, and scientific knowledge are commonly used to identify risks. Brainstorming sessions, checklists, process mapping, and cause-and-effect diagrams may also be employed. The goal of this stage is not to solve problems but to create a comprehensive list of possible risks that require further evaluation.

Risk Analysis

Risk analysis involves understanding the nature of the identified risks and estimating their magnitude. This typically includes evaluating three key factors: the likelihood (probability) that the risk will occur, the severity of its consequences if it does occur, and sometimes the detectability (ability to detect the problem before it affects the patient). For example, microbial contamination in sterile injections has low tolerance because the severity is extremely high, even if the probability is low. Quantitative methods may assign numerical scores to these factors, while qualitative methods may classify them as high, medium, or low. Tools such as FMEA are often used at this stage. Risk analysis helps prioritize risks so that attention is focused on those with the greatest potential impact.

Risk Evaluation

Risk evaluation compares the estimated risk against predefined acceptance criteria to determine whether it is tolerable or requires action. Not all risks can or need to be eliminated; some may be considered acceptable if they are sufficiently low and well controlled. Regulatory requirements, company policies, and scientific judgment guide this decision. For instance, minor cosmetic defects in tablet appearance may be acceptable if they do not affect safety or efficacy, whereas variability in drug content would be unacceptable. The outcome of risk evaluation categorizes risks into acceptable, conditionally acceptable (requiring monitoring), or unacceptable (requiring mitigation). This step ensures that resources are used efficiently by focusing on significant risks rather than trivial ones.

Risk Control

Risk control involves implementing actions to reduce risks to an acceptable level or eliminate them entirely. It includes two main components: risk reduction and risk acceptance. Risk reduction may involve modifying the manufacturing process, improving equipment design, enhancing environmental controls, strengthening

quality checks, increasing testing frequency, automating critical steps, or providing additional staff training. For example, installing HEPA filtration systems can reduce contamination risk, while automated filling machines can minimize human error. After implementing control measures, the residual risk (remaining risk) must be reassessed to confirm that it falls within acceptable limits. If not, further actions may be required. Risk control ensures that product quality is consistently maintained during routine production.

Risk Review and Communication

Risk management is not a one-time activity but a continuous process throughout the product lifecycle. Risk review involves ongoing monitoring to determine whether new risks have emerged, existing risks have changed, or control measures remain effective. This may include trend analysis of quality data, periodic audits, process performance monitoring, and review of deviations and complaints. Communication is equally important and involves sharing relevant risk information among stakeholders such as development teams, manufacturing personnel, quality assurance staff, regulatory authorities, and management. Effective communication ensures transparency, coordinated decision-making, and rapid response to potential problems. For example, if a supplier change introduces new variability, all relevant departments must be informed so that appropriate controls can be implemented.

Risk Assessment Tools

Several tools are used in QRM:

- Failure Mode and Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Hazard Analysis and Critical Control Points (HACCP)
- Fault Tree Analysis (FTA)
- Risk ranking and filtering
- Ishikawa (fishbone) diagrams

These tools help prioritize risks and guide control strategies.

Risk Assessment tool	Full Form	Purpose	Key Features	Applications in pharmaceutical
FMEA	Failure Mode and Effects Analysis	Identifies potential failure modes and their effects on product quality	Systematic, preventive, assigns risk priority number	Formulation development, manufacturing processes, equipment evaluation

FMECA	Failure Mode, Effects, and Critical Analysis	Extension of FMEA with criticality assessment	Evaluates severity, occurrence, and detectability	High risk processes, sterile products, biologics
HACCP	Hazard Analysis and Critical Control points	Identifies hazards and critical control points to prevent failures	Preventive approach, focuses on safety	Manufacturing steps, Contamination control, packaging processes
FTA	Fault Tree Analysis	Determines root causes of system failure using logical diagrams	Top-down approach, Visual representation	Equipment failure analysis, System reliability studies
Risk Ranking & Filtering	Risk Ranking and Filtering	Prioritizes risks based on predefined criteria	Compares multiple risks, decision-making tool	Resource allocation, process optimization, quality improvement
Ishikawa Diagram	Fishbone diagram	Identifies root causes of a problem	Visual brainstorming tool	Investigation of deviations, quality issues

Flow chart: 2 Risk Assessment tools

Integration of QbD and QRM

QbD and QRM are closely interconnected. Risk assessment identifies the most critical variables affecting product quality, guiding experimental design and process optimization. Continuous risk evaluation throughout the lifecycle ensures sustained product performance and compliance.

Applications in Pharmaceutical Development

QbD and QRM are applied in:

- Formulation development
- Analytical method development
- Process development and optimization
- Scale-up and technology transfer
- Continuous manufacturing
- Biopharmaceutical production

They are particularly valuable for complex dosage forms and biologics, where variability can significantly impact performance.

Benefits of QbD and Risk Management

- Improved product quality and consistency
- Enhanced process understanding
- Reduced batch failures and recalls
- Greater regulatory flexibility
- Cost savings over the product lifecycle
- Improved patient safety
- Efficient use of resources

Challenges and Limitations

Despite their advantages, implementing QbD and QRM can be challenging due to:

- High initial investment
- Need for specialized expertise
- Complex data analysis
- Organizational resistance to change
- Extensive documentation requirements

However, long-term benefits outweigh these initial difficulties.

Future Perspectives

Advancements in automation, artificial intelligence, machine learning, and digital manufacturing are expected to enhance QbD implementation. Continuous manufacturing and real-time release testing will further improve efficiency and quality assurance. Regulatory agencies increasingly support these innovations, recognizing their potential to ensure reliable medicine supply.

Conclusion

Quality by Design and Quality Risk Management represent a transformative approach to pharmaceutical development and manufacturing. By integrating scientific knowledge, systematic experimentation, and risk-based decision-making, these strategies ensure that quality is built into products from the outset. They enable robust processes, consistent product performance, regulatory compliance, and enhanced patient safety. As the pharmaceutical industry continues to evolve, QbD and QRM will remain essential tools for delivering high quality medicines efficiently and reliably.

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AI-Driven Nanomedicine for Targeted Drug Delivery

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Abstract

Nanomedicine has emerged as a transformative platform for precision therapeutics, offering the ability to engineer nanoparticles that selectively deliver drugs to disease sites while minimizing systemic toxicity. Recent advances in targeted drug delivery systems—including liposomes, polymeric nanoparticles, dendrimers, and lipid-based carriers have improved efficacy and safety profiles in oncology, infectious diseases, and chronic conditions. The integration of Artificial Intelligence (AI) into nanomedicine design, formulation optimization, and clinical translation represents a paradigm shift. Machine learning and predictive modeling facilitate rational nanocarrier design, anticipate biological interactions such as protein corona formation, optimize drug loading and release kinetics, and enable patient-specific therapeutic strategies. AI-driven approaches accelerate pre-clinical development, enhance precision medicine, and support regulatory decision-making. This chapter provides a comprehensive overview of nanocarrier platforms, passive and active targeting mechanisms, stimuli-responsive systems, and highlights the emerging role of AI in shaping the future of intelligent, personalized drug delivery.

Keywords: Nanomedicine, Targeted Drug Delivery, Nanocarriers, Artificial Intelligence, Precision Therapeutics, Stimuli-Responsive Drug Release, Rational Nanocarrier Design

Introduction

Conventional pharmacotherapy has been instrumental in controlling and eradicating many diseases; however, it suffers from several inherent limitations such as poor water solubility, low target specificity, rapid systemic clearance, limited bioavailability, and off-target toxicity. These limitations often result in suboptimal therapeutic outcomes, high systemic side effects, and increased dosing requirements that compromise patient compliance and overall treatment efficacy (Peer et al.,

2007; Mitragotri et al., 2014). In recent decades, the advent of nanotechnology has revolutionized the field of drug delivery by enabling precise control over drug distribution at the cellular and molecular levels. Nanomedicine, defined as the medical application of nanoscale materials and devices, offers unprecedented opportunities to address the shortcomings of conventional drug delivery and to engineer systems that achieve targeted, controlled, and sustained therapeutic action (Moghimi et al., 2005; Farokhzad & Langer, 2009).

Targeted drug delivery aims to enrich therapeutic levels at diseased sites while minimizing exposure to healthy tissues. Nanocarriers designed for targeted delivery exploit unique pathophysiological features of disease microenvironments—such as enhanced vascular permeability in tumors, specific receptor overexpression, and localized biochemical cues, to achieve preferential accumulation and uptake (Danhier et al., 2010; Blanco et al., 2015). This chapter reviews the fundamentals of nanomedicine, discusses major classes of nanocarriers, elucidates targeting strategies, highlights clinical and translational advances, and addresses current challenges and future prospects in the field.

Fundamentals of Nanomedicine

Definition and Scope

Nanomedicine utilizes engineered nanostructures typically in the 1–100 nm size range for diagnosis, imaging, and therapy (Rzigalinski & Strobl, 2009). Nanoparticles (NPs) possess unique size-dependent physicochemical properties that can be tuned to influence drug loading, stability, circulation half-life, and cellular interactions. Their high surface area-to-volume ratio enables surface functionalization with targeting ligands, polymers, and imaging agents, providing multifunctionality and responsiveness to biological stimuli.

Physicochemical Properties Influencing Drug Delivery

- **Particle Size and Distribution:** Size influences circulation behavior, biodistribution, and cellular uptake. Particles <10 nm often undergo rapid renal clearance, whereas those >200 nm are prone to capture by the reticuloendothelial system (RES). Particles in the 10–200 nm range strike a balance between systemic persistence and tissue extravasation (Alexis et al., 2008).
- **Surface Charge and Chemistry:** Zeta potential affects protein adsorption, colloidal stability, and interactions with cellular membranes. Neutral or slightly negative surfaces generally reduce nonspecific interactions, while cationic surfaces enhance cellular uptake but may increase toxicity (Veronese & Pasut, 2005).
- **Shape and Morphology:** Apart from size, shape (spherical, rod-shaped, discoidal) influences margination, cellular internalization, and circulation time.

Non-spherical particles exhibit differential biodistribution and cellular uptake pathways (Champion & Mitragotri, 2006).

Biological Barriers in Drug Delivery

Upon systemic administration, nanocarriers encounter physiological barriers.

- **Bloodstream and RES clearance:** Serum proteins form a protein corona that alters NP identity and facilitates opsonization.
- **Endothelial Barriers:** Tight junctions restrict passage into tissues.
- **Cellular Uptake Mechanisms:** Nanoparticles cross cellular membranes via endocytosis (clathrin-, caveolin mediated), macropinocytosis, or phagocytosis, depending on size and surface properties.
- **Endosomal Escape:** Payloads must often escape endosomal compartments to reach the cytosol or nucleus (Blanco et al., 2015; Suk et al., 2016).

Types of Nanocarriers in Drug Delivery

Nanocarriers can be broadly categorized based on composition and structure. Each platform offers distinct advantages and challenges.

Lipid-Based Nanocarriers

Liposomes were among the first nanocarriers approved for clinical use. Composed of phospholipid bilayers, liposomes can encapsulate hydrophilic agents in their core and hydrophobic drugs within the bilayer membrane. Surface modification with polyethylene glycol (PEG) enhances circulation time by reducing RES uptake (Allen & Cullis, 2013). Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) incorporate solid and liquid lipid matrices, offering enhanced drug loading and controlled release compared to traditional liposomes. These systems are biocompatible and relatively easy to scale up (Sharma et al., 2020).

Polymeric Nanoparticles

Biodegradable polymers such as polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), chitosan, and PEG are widely used to formulate nanoparticles and micelles for controlled drug release. PLGA degrades into lactic and glycolic acid, both endogenous metabolites, making it clinically attractive (Danhier et al., 2012).

Dendrimers are highly branched macromolecules with defined architecture and multiple surface functionalities, allowing high drug loading and targeting ligand conjugation (Kesharwani et al., 2015).

Inorganic Nanoparticles

Inorganic NPs offer unique optical, magnetic, and structural properties:

- **Gold Nanoparticles (AuNPs):** Used for photothermal therapy and imaging due to localized surface plasmon resonance.

- **Iron Oxide Magnetic Nanoparticles:** Employed in magnetic resonance imaging (MRI) and as stimuliresponsive carriers.
- **Silica Nanoparticles:** Provide rigid frameworks for drug loading and surface modification.

Hybrid and Smart Nanocarriers

Hybrid systems merge features of lipid, polymeric, and inorganic platforms to achieve improved performance. Stimuli-responsive nanoparticles release payloads in response to pH, temperature, redox gradients, or external triggers like light and magnetic fields (Torchilin, 2014). Such systems aim for on-demand drug release at pathological sites.

Table 1. Comparison of Major Nanocarrier Platforms

Nanocarrier Type	Composition	Drug Loading Type	Key Advantages	Major Limitations
Liposomes	Phospholipid bilayer vesicles	Hydrophilic (core), hydrophobic (bilayer)	Biocompatible; clinically validated; reduced toxicity	Possible leakage; stability concerns
Solid Lipid Nanoparticles (SLNs)	Solid lipid matrix	Mainly hydrophobic drugs	Controlled release; good tolerability	Limited drug loading capacity
Nanostructured Lipid Carriers (NLCs)	Mixture of solid and liquid lipids	Hydrophobic drugs	Improved loading over SLNs; enhanced stability	Formulation complexity
Polymeric Nanoparticles (e.g., PLGA)	Biodegradable polymers (PLGA, PCL, PEG)	Encapsulation or surface conjugation	Tunable degradation; Controlled release; versatile design	Complex manufacturing; scale-up challenges
Polymeric Micelles	Amphiphilic block copolymers	Hydrophobic core loading	Excellent solubilization; small size	Potential instability upon dilution

Dendrimers	Highly branched synthetic polymers	Surface conjugation or encapsulation	High drug loading; precise architecture	Potential cytotoxicity; high cost
Gold Nanoparticles	Metallic gold core	Surface attachment/ conjugation	Photothermal therapy; imaging capability	Long-term accumulation concerns
Magnetic Nanoparticles	Iron oxide core	Surface functionalization	Magnetic targeting; MRI imaging potential	Possible oxidative stress; aggregation risk
Silica Nanoparticles	Mesoporous silica framework	Encapsulation within pores	High loading capacity; structural stability	Biodegradability concerns

Table 1. Comparative features of nanocarrier systems used in targeted drug delivery

Targeting Strategies in Nanomedicine

Targeting increases therapeutic index by focusing drug action where it is most needed.

Passive Targeting

Passive targeting leverages the enhanced permeability and retention (EPR) effect, prominently observed in solid tumors. Hyperpermeable tumor vasculature and poor lymphatic drainage enable nanoparticles to accumulate preferentially in tumor interstitium (Maeda et al., 2013). While widely used, the EPR effect exhibits heterogeneity across cancer types and between patients, thus limiting universal efficacy (Danhier, 2016).

Active Targeting

Active targeting involves functionalizing nanoparticles with ligands that recognize overexpressed receptors on diseased cells (antibodies, peptides, aptamers). Examples include: Folate receptors targeted by folate-conjugated carriers, transferrin receptors utilized for brain and tumor targeting, antibody-drug conjugated nanoparticles for specific cancer antigens (Huang et al., 2020).

This approach enhances cellular internalization via receptor-mediated endocytosis and improves selectivity (Muro, 2012).

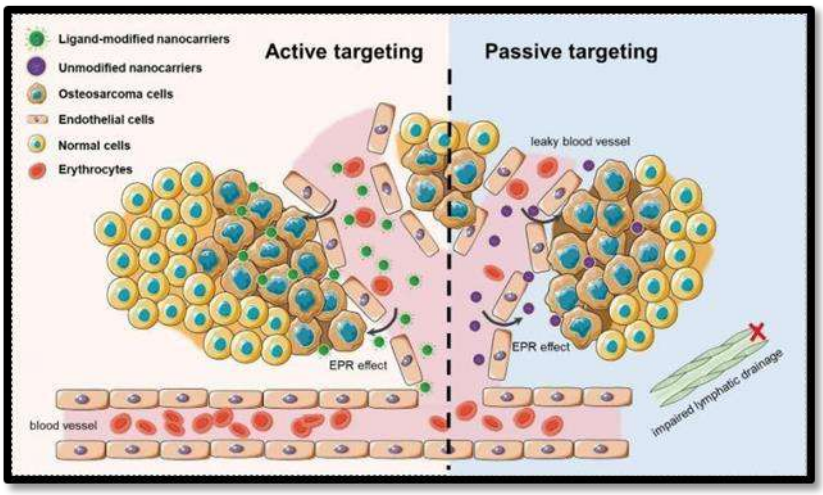

Figure 1. Active vs Passive Targeting

Comparison of passive targeting via enhanced permeability and retention (EPR) effect and active targeting using ligand–receptor interactions (antibody-, peptide-, and folatemediated endocytosis).

Stimuli-Responsive Targeting

Stimuli-responsive systems exploit intrinsic cues (pH, redox potential, enzymes) or external triggers (light, magnetic field) for controlled drug release:

- pH-responsive nanoparticles release payloads in acidic tumor or endosomal environments.
- Redox-sensitive linkers cleave in high glutathione concentrations inside cells.
- Thermo-responsive polymers change configuration with temperature changes (Liu et al., 2014).

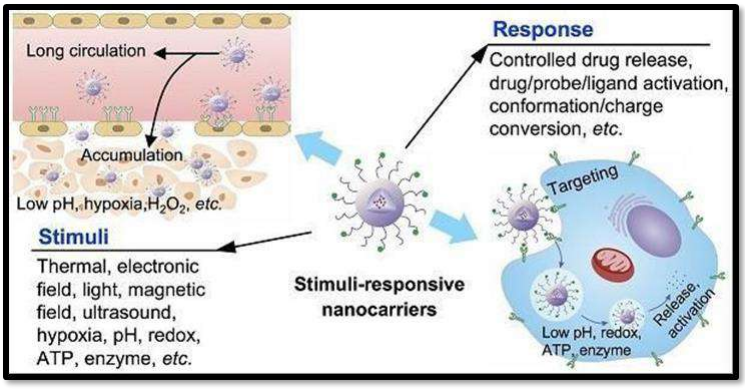

Figure 2: Stimuli-responsive targeting

Stimuli-responsive nanocarriers designed to releasetherapeutic agents in response to Internal (pH, redox, enzymes) and external (temperature, light, magnetic field) triggers, enabling targeted and controlled drug delivery to diseased tissues.

Artificial Intelligence in Nanomedicine and Drug Delivery

Artificial Intelligence (AI) is rapidly transforming nanomedicine by enabling rational design, optimization, and predictive modeling of targeted drug delivery systems. Traditional nanocarrier development relies heavily on trial-and-error experimentation, which is time-consuming, resource-intensive, and often poorly predictive of clinical success. AI—particularly machine learning (ML), deep learning (DL), and computational modeling— offers the ability to analyze large experimental and clinical datasets to inform decisions on nanoparticle composition, drug loading, targeting ligands, and patient-specific therapy.

The integration of AI allows researchers to move from empirically driven design to data-driven, predictive nanomedicine, bridging the gap between bench-scale development and clinical translation.

AI-guided nanocarrier design

- **Prediction of Physicochemical Properties:** Machine learning algorithms can predict nanoparticle characteristics critical for drug delivery, including:
  - Particle size and size distribution
  - Surface charge (zeta potential)
  - Drug loading capacity
  - Encapsulation efficiency
  - Drug release kinetics
  - Stability under physiological conditions
- **Optimization of Drug-Carrier Compatibility:** AI models can analyze molecular descriptors, hydrophobicity indices, and chemical properties to:
  - Select the optimal nanocarrier for a given drug
  - Predict stability in systemic circulation
  - Minimize premature release or degradation

AI in biological interaction prediction

Protein Corona Modeling

When nanoparticles enter biological fluids, proteins adsorb onto their surface, forming a protein corona, which alters circulation, biodistribution, and immune recognition. AI can:

- Predict corona composition based on nanoparticle physicochemistry and plasma proteomics
- Assess impact on targeting efficiency
- Anticipate clearance by the reticuloendothelial system

Predicting Biodistribution and Pharmacokinetics

AI-driven physiologically based pharmacokinetic (PBPK) models integrate:

- Nanoparticle properties

- Organ-specific tissue permeability
- Patient-specific physiological parameters
- To predict: Tumor accumulation, Off-target organ deposition, Clearance rates.

AI in Toxicity and Immunogenicity Prediction

Nanotoxicity remains a major translational hurdle. AI models trained on nanotoxicology databases can predict:

- Cytotoxic effects
- Oxidative stress potential
- Hemolysis risk
- Immunogenic responses

AI in personalized and precision nanomedicine

Patient-Specific Targeting

AI integrates genomic, proteomic, and imaging datasets to:

- Identify overexpressed tumor receptors
- Select optimal ligands for active targeting
- Predict tumor heterogeneity and response to therapy

Digital Twin Modeling

Emerging approaches use AI to construct digital twins—virtual patient models simulating:

- Nanoparticle circulation
- Tumor penetration
- Drug release kinetics
- Therapeutic outcomes

AI in Clinical Translation and Regulatory Science

- **Clinical Trials:** AI predicts trial outcomes, identifies patient subgroups likely to respond, and optimizes dosing schedules.
- **Manufacturing:** AI-driven process control ensures batch-to-batch reproducibility and quality.
- **Regulatory:** Predictive algorithms support documentation of nanoparticle characterization, stability, and safety data for submission to regulatory authorities. This integration reduces both time-to-market and clinical risk.

AI in Advanced Therapeutic Modalities

AI is increasingly applied to next-generation nanomedicine, including:

- mRNA vaccines (e.g., lipid nanoparticle optimization)
- siRNA and CRISPR/Cas9 delivery systems
- Theranostics (integrated imaging + therapy)

- Smart stimuli-responsive carriers that adapt to tumor microenvironment cues

Challenges of AI integration

While AI offers immense potential, challenges remain:

- Lack of large, standardized datasets for training
- Reproducibility issues across laboratories
- Black-box algorithms with limited interpretability
- Regulatory uncertainties for AI-driven designs
- Ethical concerns regarding data privacy and algorithmic bias

Applications of Targeted Nanomedicine

Cancer Therapy

Cancer has been the primary focus of targeted nanomedicine due to the EPR effect and distinct tumor microenvironment. Nanocarriers deliver chemotherapeutics, gene therapies, immunomodulators, or combinations thereof. Multifunctional platforms enable theranostics, integrating imaging and therapy for real-time monitoring (Rosi et al., 2006; Shi et al., 2017).

Emerging strategies integrate nanomedicine with immunotherapy, such as delivering immune checkpoint inhibitors or adjuvants to lymphoid organs to enhance antitumor immunity (Tang et al., 2014).

Infectious Diseases

Nanocarriers improve treatment of intracellular infections by facilitating delivery of antimicrobial agents into host cells. For diseases such as tuberculosis and HIV, targeted carriers enhance intracellular bioavailability and overcome resistance mechanisms (Singh & Lillard, 2009).

Neurological Disorders

Crossing the blood–brain barrier (BBB) has been a longstanding challenge. Nanoparticles can traverse the BBB via receptor-mediated transcytosis or transient disruption methods. This capability holds promise for treating neurodegenerative disorders like Alzheimer's and Parkinson's disease, delivering neuroprotective agents or genetic cargoes (Saraiva et al., 2016).

Cardiovascular and Inflammatory Diseases

Inflammatory microenvironments exhibit altered vascular permeability and receptor expression. Nanoparticles targeting inflamed endothelium can deliver anti-inflammatory drugs to atherosclerotic plaques, reducing progression and complication risk (Beldman et al., 2017).

Challenges and Limitations

While promising, targeted nanomedicine encounters obstacles:

- **Biological Heterogeneity:** Variable EPR effect and receptor expression across patients.
- **Protein Corona Formation:** Alters nanoparticle identity and targeting efficacy.
- **Immunogenicity:** PEG and other polymers may elicit immune responses.
- **Cost and Complexity:** Advanced nanocarriers are expensive to produce and characterize (Longmire et al., 2008; Wilhelm et al., 2016).

Future Perspectives

The future of targeted nanomedicine is poised to be shaped by the convergence of advanced materials science, systems biology, and artificial intelligence-driven design, moving the field toward truly personalized and adaptive therapeutics. Next-generation nanocarriers will increasingly be engineered as multifunctional, stimuli-responsive, and self-regulating systems capable of sensing disease microenvironment cues—such as pH, redox gradients, enzymatic activity, and hypoxia—and responding with controlled, on-demand drug release. Integration of AI and machine learning will transition nanomedicine from empirical formulation strategies to predictive, data-driven design frameworks, enabling optimization of nanoparticle composition, surface functionalization, pharmacokinetics, and safety profiles prior to experimental validation. AI-powered physiologically based pharmacokinetic (PBPK) modeling and digital twin simulations will allow individualized dosing strategies by incorporating patient-specific genomic, proteomic, and imaging data, thereby enhancing therapeutic precision while minimizing systemic toxicity. Advances in nanocarrier-enabled delivery of gene-editing tools (such as CRISPR/Cas systems), mRNA therapeutics, RNA interference platforms, and combination immunotherapies will expand the therapeutic landscape beyond conventional chemotherapeutics. Furthermore, smart theranostic nanoparticles combining real-time imaging and therapy will facilitate dynamic monitoring of treatment response and adaptive clinical decision-making. Scalable manufacturing technologies, standardized characterization protocols, and AI-assisted quality control systems are expected to improve reproducibility and regulatory acceptance. As interdisciplinary collaboration deepens among clinicians, material scientists, computational biologists, and regulatory agencies, nanomedicine is likely to evolve into a cornerstone of precision medicine— offering patient-tailored, safer, and more effective therapeutic interventions across oncology, infectious diseases, neurological disorders, and chronic inflammatory conditions.

Conclusion

Nanomedicine represents a transformative paradigm in modern therapeutics by overcoming fundamental limitations of conventional pharmacotherapy, including poor bioavailability, nonspecific distribution, rapid clearance, and systemic toxicity.

Through rational engineering of lipid-based, polymeric, inorganic, and hybrid nanocarriers, targeted drug delivery systems can achieve controlled, site-specific, and sustained therapeutic action while minimizing damage to healthy tissues. The incorporation of passive, active, and stimuli-responsive targeting strategies has significantly enhanced therapeutic indices, particularly in oncology, infectious diseases, neurological disorders, and inflammatory pathologies. Importantly, the integration of artificial intelligence into nanomedicine design and translation marks a critical evolution in the field, shifting from trial-and-error experimentation toward predictive, data-driven development. AI facilitates optimization of nanoparticle physicochemical properties, prediction of biological interactions such as protein corona formation, modeling of biodistribution and pharmacokinetics, toxicity forecasting, and patient-specific therapeutic planning. Despite ongoing challenges—including biological heterogeneity, protein corona effects, immunogenicity, scalability issues, and regulatory complexities—continuous innovation in materials science, computational modeling, and translational research is steadily addressing these barriers. As nanotechnology and artificial intelligence converge, the future of drug delivery lies in intelligent, adaptive, and personalized nanotherapeutic systems capable of dynamically responding to individual patient biology. Collectively, these advancements position AI-driven nanomedicine as a foundational pillar of next-generation precision healthcare, with the potential to redefine disease management and significantly improve global health outcomes.

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Personalized and Precision Medicine

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Abstract

Personalized and precision medicine represent transformative approaches in modern healthcare, shifting from generalized treatment models to more targeted and individualized strategies. This chapter examines the conceptual distinctions and overlaps between these paradigms, emphasizing their foundations in genomics, bioinformaticsand molecular diagnostics. It explores key enabling technologies, including next-generation sequencing, pharmacogenomicsand artificial intelligence, which facilitate patient stratification and optimized therapeutic interventions. The chapter further highlights clinical applications across oncology, cardiology, neurologyand infectious diseases, demonstrating improved diagnostic accuracy and treatment outcomes. Additionally, it addresses critical ethical, legaland social implications, such as data privacy, equity of accessand genetic discrimination. Despite notable advancements, challenges including high costs, data complexityand limited diversity in genomic databases persist. The chapter concludes by discussing future directions, underscoring the potential of integrated multi-omics and digital health technologies to advance precision healthcare and research innovation.

Keywords: Personalized Medicine, Precision Medicine, Genomics, Pharmacogenomics, Molecular Diagnostics.

Introduction

The evolution of modern medicine has been marked by a gradual shift from generalized therapeutic approaches toward more individualized care strategies. Traditional medical practices have largely relied on standardized treatments designed for the "average patient," often overlooking inter-individual variability in genetics, environmentand lifestyle. In contrast, personalized and precision medicine represent transformative paradigms that aim to tailor healthcare interventions to the unique biological characteristics of each individual.

Personalized medicine broadly refers to the customization of healthcare, wherein medical decisions and treatments are adapted to individual patient characteristics. Precision medicine, often used interchangeably but conceptually distinct, emphasizes the classification of individuals into subpopulations based on genetic, biomarker, phenotypic, or psychosocial characteristics. These approaches are underpinned by advances in genomics, bioinformaticsand systems biology, which have enabled a deeper understanding of disease mechanisms at the molecular level.
This chapter explores the conceptual foundations, technological advancements, applications, challengesand future directions of personalized and precision medicine, with a focus on their implications for research and clinical practice.

Conceptual Framework and Definitions

- **Personalized Medicine**

Personalized medicine involves tailoring medical treatment to the individual characteristics of each patient. This includes genetic makeup, medical history, environmental exposuresand lifestyle factors. The goal is to optimize therapeutic efficacy while minimizing adverse effects.Historically, personalization in medicine was limited to observable characteristics such as age, weightand comorbidities. However, with the advent of genomic technologies, personalization now extends to molecular-level interventions.

- **Precision Medicine**

Precision medicine refines the concept of personalization by focusing on identifying subgroups of patients who share specific biological markers. Rather than creating a unique treatment for every individual, precision medicine seeks to stratify populations into groups that respond similarly to particular interventions.

- **Distinction and Overlap**

While often used interchangeably, the distinction lies in scope:

- **Personalized Medicine:** individual-focused customization
- **Precision Medicine:** subgroup-based stratification

Both approaches converge in their shared goal of improving treatment outcomes and advancing evidence-based care.

Table 1: Comparison Between Personalized Medicine and Precision Medicine

Aspect	Personalized Medicine	Precision Medicine
Definition	Tailors' treatment to individual patients	Classifies patients into subgroups based on biomarkers
Focus	Individual-level customization	Group-level stratification
Data Basis	Genetic, lifestyle, environmental factors	Genomic and molecular profiling

Aspect	Personalized Medicine	Precision Medicine
Approach	Holistic and patient-centric	Data-driven and classification-based
Clinical Application	Broad across all medical fields	Highly prominent in oncology and rare diseases
Example	Adjusting drug dosage based on patient metabolism	Targeted cancer therapy based on gene mutation

Technological Foundations

The implementation of personalized and precision medicine has been facilitated by rapid advancements in several key technological domains.

- **Genomics and Next-Generation Sequencing**

The completion of the Human Genome Project and subsequent developments in next-generation sequencing (NGS) have revolutionized biomedical research. These technologies allow for rapid and cost-effective sequencing of entire genomes, enabling the identification of genetic variants associated with disease susceptibility and drug response.

- **Bioinformatics and Big Data Analytics**

The integration of large-scale biological data requires sophisticated computational tools. Bioinformatics plays a crucial role in analyzing genomic, proteomicand metabolomic datasets. Machine learning and artificial intelligence further enhance predictive modeling and decision-making processes.

- **Biomarkers and Molecular Diagnostics**

Biomarkers are measurable indicators of biological processes or responses to therapeutic interventions. Molecular diagnostics enable early detection, disease classificationand monitoring of treatment efficacy. Examples include genetic mutations in cancer and protein biomarkers in cardiovascular diseases.

- **Pharmacogenomics**

Pharmacogenomics examines how genetic variations influence drug metabolism and response. This field has significant implications for reducing adverse drug reactions and optimizing drug selection and dosage.

Table 2: Key Technologies Enabling Precision Medicine

Technology	Description	Application Example
Genomics	Study of entire genome	Identifying disease-associated mutations
Next-Generation	High-throughput DNA	Cancer genome profiling

Technology	Description	Application Example
Sequencing	sequencing	
Bioinformatics	Computational analysis of biological data	Predictive disease modeling
Pharmacogenomics	Study of gene-drug interactions	Personalized drug dosing
Molecular Diagnostics	Detection of specific biomarkers	Early disease diagnosis
Artificial Intelligence	Machine learning for data interpretation	Clinical decision support systems

Applications in Clinical Practice

- **Oncology**

Cancer treatment has been at the forefront of precision medicine. Targeted therapies, such as those directed at specific genetic mutations, have significantly improved outcomes in various cancers. For example, therapies targeting HER2 in breast cancer or EGFR mutations in lung cancer demonstrate the effectiveness of biomarker-driven interventions.

- **Cardiovascular Diseases**

Genetic profiling can identify individuals at risk for cardiovascular diseases, enabling early intervention. Precision medicine approaches also guide the use of anticoagulants and lipid-lowering therapies based on genetic predisposition.

- **Neurological Disorders**

In conditions such as Alzheimer's disease and epilepsy, precision medicine aids in understanding disease heterogeneity and tailoring treatment strategies. Genetic testing can inform diagnosis and prognosis.

- **Infectious Diseases**

Precision medicine has played a critical role in managing infectious diseases by identifying pathogen-specific characteristics and host responses. This approach enhances vaccine development and antimicrobial therapy.

Table 3: Applications of Precision Medicine in Different Domains

Medical Field	Application	Outcome/Benefit
Oncology	Targeted therapy based on tumor genetics	Improved survival rates
Cardiology	Genetic risk prediction	Early intervention
Neurology	Personalized treatment for epilepsy	Better seizure control
Infectious	Pathogen-specific treatment	Reduced drug resistance

Medical Field	Application	Outcome/Benefit
Diseases		
Rare Diseases	Gene-based diagnosis	Accurate and early diagnosis

Ethical, Legal and Social Implications (ELSI)

The integration of personalized and precision medicine raises several ethical and societal concerns.

- **Data Privacy and Security**

The collection and storage of genetic data pose significant risks related to privacy breaches. Ensuring secure data management and informed consent is essential.

- **Equity and Access**

There is a growing concern that precision medicine may exacerbate healthcare disparities, as advanced technologies may not be equally accessible across populations.

- **Genetic Discrimination**

The misuse of genetic information by employers or insurance companies could lead to discrimination. Regulatory frameworks are necessary to safeguard individuals.

- **Informed Consent and Autonomy**

Patients must be adequately informed about the implications of genetic testing, including potential psychological impacts and incidental findings.

Challenges and Limitations

Despite its promise, personalized and precision medicine face several challenges:

- High cost of genomic testing and data infrastructure
- Limited integration into clinical workflows
- Lack of standardized guidelines
- Insufficient representation of diverse populations in genomic databases
- Complexity of interpreting multi-omics data

These challenges highlight the need for interdisciplinary collaboration and policy development.

Future Directions

The future of personalized and precision medicine lies in the integration of multi-omics data, real-world evidence and digital health technologies. Advances in wearable devices, electronic health records and telemedicine will further enhance individualized care. Emerging areas such as gene editing, particularly CRISPR-based technologies, hold potential for curative interventions. Additionally, the use

of artificial intelligence in predictive analytics will revolutionize disease prevention and management.

Collaborative initiatives and global data-sharing platforms will be critical in overcoming current limitations and ensuring equitable access to precision healthcare.

Conclusion

Personalized and precision medicine represent a paradigm shift in healthcare, moving from reactive to proactive and predictive models of care. By leveraging advancements in genomics, bioinformatics and molecular diagnostics, these approaches offer the potential to improve clinical outcomes, reduce adverse effects and enhance patient satisfaction.

However, realizing this potential requires addressing ethical, legal and logistical challenges, as well as ensuring equitable access to emerging technologies. For research scholars, this field presents vast opportunities for interdisciplinary research and innovation, shaping the future of medicine in the 21st century.

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Formulation and Evaluation of Herbal Chewable Tablets as an Iron Supplement

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Abstract

Chewable tablets are intended to be chewed before swallowing and are especially suitable for children and elderly patients who have difficulty swallowing intact tablets. They are also useful for administering high-dose drugs. In this study, *Sonchas asper* (SA) and *Memecylon umbellatum* (MU) were selected as natural iron sources. Phytochemical screening confirmed the presence of flavonoids, saponin glycosides, proteins, and iron in both plants. Iron content was determined using acid digestion and spectrophotometric methods, showing 8.5% in SA and 2.3% in MU, indicating higher iron content in SA.Granules were prepared by the wet granulation method and evaluated. Chewable tablets containing a combination of SA and MU were formulated and tested. Each tablet contained 10 ± 0.2 mg of iron, confirmed by spectrophotometric analysis. Formulation A was found to be most suitable due to its shorter disintegration time. It was observed that decreasing hydroxypropyl cellulose (HPC) increased disintegration time. Overall, both plant sources are suitable for treating iron deficiency, with SA being richer in iron. Their antioxidant properties may also help in managing blood-related disorders.

Keyword: Chewable Tablets, Iron Supplement, Sonchus asper (SA), *Memecylon umbellatum* (MU), Herbal Drugs, Iron Deficiency, Spectrophotometric Method, Atomic Absorption, Wet Granulation, Disintegration Time, In-vitro Dissolution, HPC (Hydroxypropyl Cellulose), Antioxidant Activity, Natural Iron Sources.

Introduction

The goal of any drug delivery system is to deliver a therapeutic amount of drug to the desired site, achieve the required concentration promptly, maintain it for a suitable duration, and minimize adverse effects. For decades, drugs have been administered using various dosage forms such as tablets, capsules, liquids, creams, aerosols, and injectables. Among these, the oral route is the most preferred and widely used, accounting for nearly 90% of systemic drug delivery due to its convenience, ease of administration, flexibility in formulation, and cost-effectiveness.

Chewable tablets are designed to be chewed before swallowing and are not intended to be swallowed whole. They provide an effective unit dosage form, especially for children and elderly patients who may have difficulty swallowing conventional tablets. They also help achieve a faster onset of action and are suitable for high-dose drugs.Iron is an essential trace element required for the formation of hemoglobin and proper oxygen transport in the body. The body loses iron daily through normal processes such as excretion, sweating, and shedding of skin cells, and additional losses occur through bleeding. To maintain adequate levels, an average intake of about 18 mg of iron per day is recommended, with higher requirements during conditions like pregnancy. Dietary sources of iron include red meat, liver, egg yolk, beans, nuts, and fortified cereals. Insufficient iron leads to iron deficiency anemia, characterized by fatigue, weakness, and pale skin due to reduced hemoglobin levels. This condition can be effectively treated with iron supplementation.

Common types of anemia include iron deficiency anemia, thalassemia, aplastic anemia, hemolytic anemia, sickle cell anemia, pernicious anemia, and Fanconi anemia.

Experimental

- **Plant Authentication:** *Sonchus asper* and *Memecylon umbellatum* were authenticated, and herbarium specimens were deposited.
- **Collection of Plant Material:** *Memecylon umbellatum* was collected from Gaganbavada and sun-dried, while aerial parts of Sonchus asper were collected during flowering season and shade-dried.
- **Powdering:** *Sonchus asper* was powdered and passed through sieve No. 40#, and *Memecylon umbellatumthroughsieve* No.80#.
- **Extraction:** Extraction was performed by maceration using methanol, chloroform water, chloroform, and dichloromethane.

- **Procedure:** Powdered drug (1 g) was mixed with 100 ml solvent, shaken for 52 hours, filtered, and dried.
- **Drying of Extract:** Extracts were dried at 50°C for 48 hours, stored in a desiccator, and extractive values were calculated.

Phytochemical screening of SADE and MUDE

Sr. No.	Phytochemical Constituent	Tests Performed	Observation / Result
1	Alkaloids	a) Dragendorff's test b) Mayer's test c) Wagner's test	Presence indicated by characteristic precipitate
2	Flavonoids	a) Shinoda test b) Lead sulphuric acid test c) Acetate solution test d) Sodium hydroxide test	Color change confirms presence
3	Tannins& Phenolic Compounds	a) Lead acetate test b) Bromine water test c) Potassium dichromate test d) Dilute nitric acid test	Formationof precipitate/color change
4	Saponin Glycosides	a) Foam test b) Hemolytic test	Stablefoam/ hemolysis indicates presence
5	Proteins	a) Biuret test b) Millon's test c) Xanthoproteic test	Color reactions confirm proteins
6	Iron	Extract + 2 drops HCl + pure aspirin	Violet color formation indicates presence of iron

Extraction on Large Scale: Methanol was selected for large-scale extraction by maceration. About 50 g powder of Sonchus asper and Memecylon umbellatum was soaked in 500 ml methanol and kept in an orbital shaker for 52 hours at 50 rpm. The solution was filtered and the filtrate was dried.

UV–Visible Spectroscopy (Determination of λmax): UV spectra of SADE and MUDE were obtained using a Jasco V-630 spectrophotometer. A 1 µg/ml solution in methanol was scanned from 200–800 nm, and λmax was determined.

Calibration Curve (SADE & MUDE): Calibration curves were prepared using ferrous sulphate (10–50 µg/ml) in methanol, distilled water, 0.1 N HCl, and phosphate buffer pH 7.4. Hydroxylamine HCl and o-phenanthroline were added to form an orange-red complex, and absorbance was measured at 511 nm.

Preformulation Studies: Preformulation included melting point, solubility, and iron estimation.

Melting Point Determination: Measured by capillary method using paraffin oil bath, and average of three readings was recorded.
Solubility Study: Solubility was tested in different solvents by shaking samples for 48 hours at 30±2°C and analyzed using UV spectrophotometry.

Estimation of Iron

- **Acid Digestion / Atomic Absorption Method:** For Sonchus asper and Memecylon umbellatum, 1 g dry extract was digested with a mixture of perchloric, nitric, and sulphuric acids for 10 minutes or until fumes ceased. The mixture was filtered, diluted to 10 ml with double distilled water, further diluted as required, and analyzed using an atomic absorption spectrometer. Results were reported as average of triplicates.
- **Spectrophotometric Method:** Ferrous sulphate was dissolved in phosphate buffer pH 7.4 and diluted. Hydroxylamine hydrochloride and o-phenanthroline were added to form an orange-red complex. After 45 minutes, absorbance was measured at 511 nm using a UV-Visible spectrophotometer.
- **Formulation Design:** Three batches of chewable tablets (A to C) were prepared by direct compression method.

Table: Composition of chewable tablet of SADE and MUDE

Batch code	SA mg	MU mg	HPC mg	Mannitol mg	Aspartame mg	Xanthan gum mg	MS mg	Aerosol mg	Starch paste
A	100	200	50	50	2	80	2.3	15	qs
B	100	200	40	50	2	85	2.3	15	qs
C	100	200	30	50	2	90	2.3	15	qs

- **Preparation of Granules:** The drug and excipients were mixed, and starch was added as a granulating agent. The wet mass was passed through sieve No. 44, dried for 1 hour, and re-sieved through No. 10. Fines were calculated.
- **Evaluation of Granules:** Granules were evaluated for their properties. Bulk density was determined by measuring volume and weight, tapped density by

recording minimum volume after tapping, and angle of repose by fixed funnel method to assess flowability.

Different ranges of flowability in terms of angle of repose are given below.

Table: Relationship between angle of repose (θ) and flow properties

Angle of repose (θ)°	**Flow**
Less than 25	Excellent
25-30	Good
30-40	Satisfactory
40-50	Poor
Greater than 50	Very poor

Carr's compressibility index and Hausner's ratio: Granules of all the batches were evaluated for Carr's compressibility index (CCI) and Hausner's ratio (HR). Bulk density apparatus was used for tapping (Lab Hosp, Mumbai, Maharashtra, India).

$$CCI = \frac{(TD - BD)}{TD} \times 100 \quad HR = \left(\frac{TD}{BD}\right)$$

Where, TD and BD are tapped density and bulk density respectively.

Table: Grading of the granules for their flow properties according to Carr's Index

Consolidation Index (Carr %)	**Flow**
5-12	Excellent
12-16	Good
18-21	Fair
23-28	Poor
28-35	Poor
35-38	Very poor
>40	Extremely Poor

Preparation of Chewable Tablets: Chewable tablets were prepared using a physical mixture with suitable excipients by the wet granulation method. The

ingredients were mixed properly, and starch was added as a granulating agent. The wet mass was passed through sieve No. 44, dried in a hot air oven for 1 hour, and then passed through sieve No. 10. Finally, the granules were compressed using a Rimek tablet punching machine with a 10 mm punch.

Evaluation of Chewable Tablets: The chewable tablets were evaluated for following test parameters.

Hardness: Tablet hardness (crushing strength) was measured using a Monsanto hardness tester, and values were recorded in triplicate in kg/cm².

Weight Variation: Twenty tablets were weighed, and individual weights were compared with the average to assess uniformity.

Friability: Ten tablets were tested in a friabilator at 25 rpm for 4 minutes, and percentage weight loss was calculated. Values below 1% were acceptable.

Disintegration Time: Determined using a disintegration apparatus in pH 7.4 medium at 37±2°C, and time for complete disintegration was recorded.

Dissolution Studies: Conducted using USP II apparatus in methanol at 37±0.5°C and 50 rpm. Samples were withdrawn at intervals, treated with reagents, and analyzed using a UV spectrophotometer to ensure uniform drug release.

Table: Summary of general dissolution conditions

Parameter	**Specifications**
Dissolution medium	900 ml methanol
Temperature	37ºC±0.5ºC
Rotation speed	50 rpm
Volume withdrawn	5 ml every 2 minutes
□max	341 nm
Dilution factor	5 ml
Tablet taken	1 tab (known drug content)

Characterization of Optimized Formulation (Estimation of Iron)

- **Acid Digestion Method:** Tablets equivalent to 1 g extract were digested with a mixture of perchloric, nitric, and sulphuric acids, filtered, diluted, and analyzed

for iron content using atomic absorption spectrophotometry. Results were reported as average of triplicates.

- **Spectrophotometric Method:** Tablets equivalent to 1 g extract were dissolved in phosphate buffer pH 7.4, treated with hydroxylamine hydrochloride and o-phenanthroline to form an orange-red complex, and absorbance was measured at 511 nm.
- **Stability Study:** Stability testing was performed as per FDA and ICH guidelines at 25°C/60% RH and 40°C/75% RH for 6 months, with intermediate testing at 30°C/75% RH if required.

Table: ICH guidelines for stability studies

Conditions	Temperature	Duration
Freezer conditions	−20 to –10ºC	-
Refrigerator	2 to 8ºC	-
Controlled room temperature	15 to 30ºC	Till expiry date
Accelerated temperature	40 to 50ºC	6 months.

Stability Studies: Stability studies of SADE and MUDE chewable tablets were conducted at 45°C/75% RH for 1 month. Tablets were evaluated for hardness, disintegration, dissolution, and physical parameters at 10, 20, and 30 days.

Result and Discussion

Plant Authentication: Sonchus asper and Memecylon umbellatum were authenticated, and herbarium specimens were deposited.

Collection, Powdering and Extraction: Sonchus asper and Memecylon umbellatum were collected, powdered, and extracted using methanol, chloroform water, chloroform, and dichloromethane.

Fig. Plant and Powder of *Sonchus asper*

Fig. Plant and Powder of Memecylon umbellatum bark

Determination of Extractive Value

Table: Percent Extractive values

Sr. no	Plant name	Solvents			
		Methanol	**Chloroform**	**Chloroform water**	**Dichloromethane**
1	*Sonchus asper*	14.68	4.12	10.17	1.30
2	*Memecylon umbellatum*	15.42	2.83	14.74	1.48

Preliminary Phytochemical Screening: Preliminary phytochemical screening of SADE showed the presence of alkaloids, flavonoids, tannin, phenolic compounds, saponin glycosides and vitamins. In flavonoids predominantly flavonols, dihydro derivative, xanthenes and flavones have been reported.

Table: Preliminary phytochemical tests for SADE

Name of test	Result		Name of test	Result	
	+	-		+	-
Test for alkaloids			**Test for flavonoids**		
Dragandroffs test	+		Shinoda test	+	
Mayers test	+		Lead acetate test	+	
Wagners test	+		Hydrochloric acid test	+	
Test for saponin glycoside			Sodium hydroxide test	+	
Foam test	+		**Test for tannin and phenolic compounds**		
Hemolytic test	+		Lead acetate test	+	
Test for proteins	+		Bromine water test	+	
Biuret test	+		Potassium dichromate test	+	
Ninhydrin test	+		Dilute HNO_3	+	
Xanthoprotic test	+		5% $FeCl_3$	+	
Test for iron	+				

From the test it confirms the presence of alkaloids, saponins flavonoids proteins, tannin, phenolic compounds and iron.Preliminary phytochemical screening of MUDE showed the presence of alkaloids, flavonoids, tannin, phenolic compounds, saponin glycosides and vitamins. In flavonoids predominantly flavonols, dihydro derivative, xanthenes and flavones have been reported.

Table: Preliminary phytochemical tests for MUDE.

Name of test	**Result**		**Name of test**	**Result**	
	+	-		+	-
Test for alkaloids			**Test for flavonoids**		
Dragandroffs test		-	Shinoda test	+	
Mayers test		-	Lead acetate test	+	
Wagners test		-	Hydrochloric acid test	+	
Test for saponin glycoside			Sodium hydroxide test	+	
Foam test	+		**Test for tannin and phenolic compounds**		
Hemolytic test	+		Lead acetate test	+	
Test for proteins	+		Bromine water test	+	
Biuret test	+		Potassium dichromate test	+	
Ninhydrin test	+		Dilute HNO_3	+	
Xanthoprotic test	+		5% $FeCl_3$	+	
Test for iron	+				

From the test it confirms the absence of alkaloids and the presence of saponins flavonoids proteins, tannin, phenolic compounds and iron.

UV – visible spectroscopy (Determination of λ max)

UV spectra of SADE: From the UV spectroscopy, λ max of SADE in methanol was found to be 341nm.

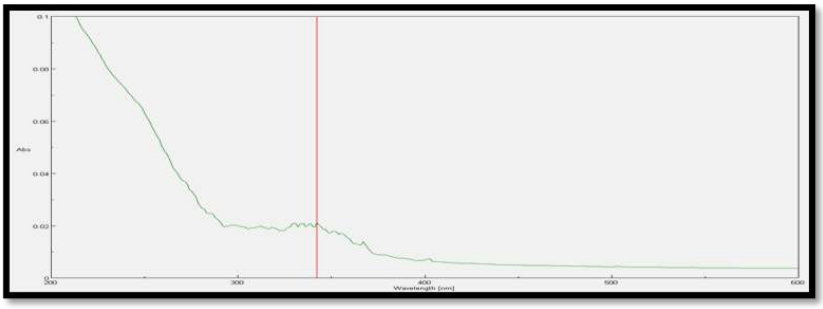

Fig. UV Spectra of SADE in methanol

UV spectra of MUDE

From the UV spectroscopy, λ max of MUDE in methanol was found to be 250nm.

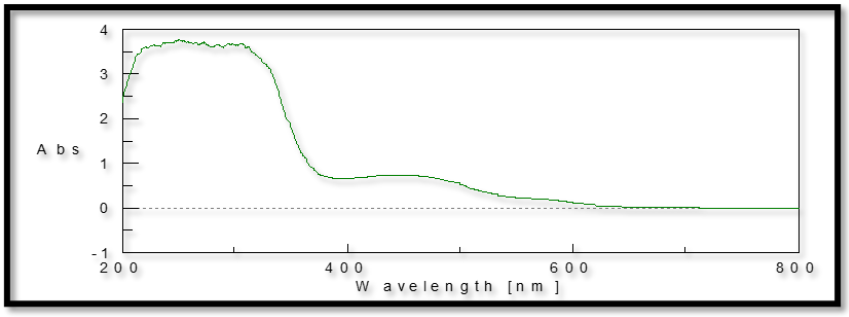

Fig. UV Spectra of MUDE methanol

Calibration curve of SADE for different solvents

Calibration Curve in Methanol: The absorbance values at different concentration obtained by double beam spectrophotometer (JascoV630) are given in Table. Using absorbance and concentration data the calibration curve was plotted as shown in Fig. The graph of absorbance Vs concentration was appeared to be linear in the concentration range of 10–50µg/ml at 314nm. Obey Beer-Lambert's law in the range of 10–50µg /ml.

Table: Calibration curve SADE in methanol

Concentration(µg/ml)	Absorbance at 341 nm
0	0
10	0.0128
20	0.0223
30	0.0301
40	0.0368
50	0.0436

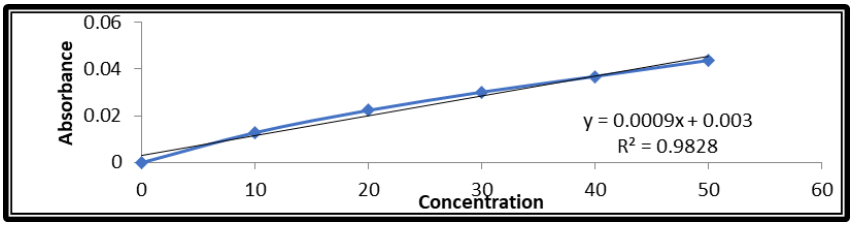

Fig. Calibration curve SADE in methanol

Calibration Curve of SADE in Double Distilled Water

The absorbance values at different concentration obtained by double beam spectrophotometer (JascoV630) are given in Table. Using absorbance and concentration data the calibration curve was plotted as shown in Fig. The graph of

absorbance Vs concentration was appeared to be linear in the concentration range of 10–50µg/ml at 314nm. Obey Beer-Lambert's law in the range of 10–50µg /ml.

Table: Calibration curve SADE in double distilled water

Concentration(µg/ml)	Absorbance at 341 nm
0	0
10	0.0168
20	0.0272
30	0.0378
40	0.0499
50	0.0589

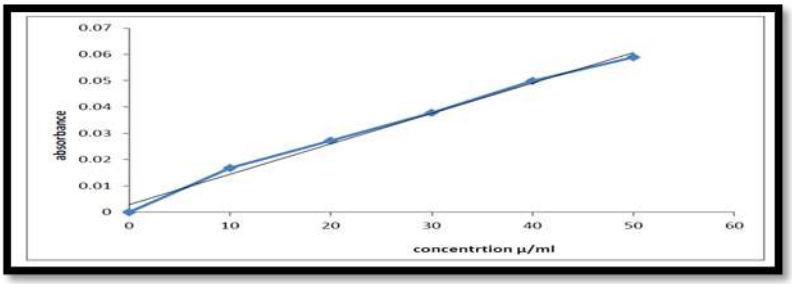

Fig. Calibration curve SADE in double distilled water

Calibration Curve of SADE in 0.1N HCl: Absorbance values at different concentrations were measured using a UV double beam spectrophotometer (Jasco V-630). The calibration curve plotted between absorbance and concentration showed a linear relationship in the range of 10–50 µg/ml at 314 nm, obeying Beer-Lambert's law.

Table: Calibration curve SADE in 0.1N HCl

Concentration(µg/ml)	Absorbance at 341 nm
0	0
10	0.0014
20	0.0031
30	0.0054
40	0.0076
50	0.0099

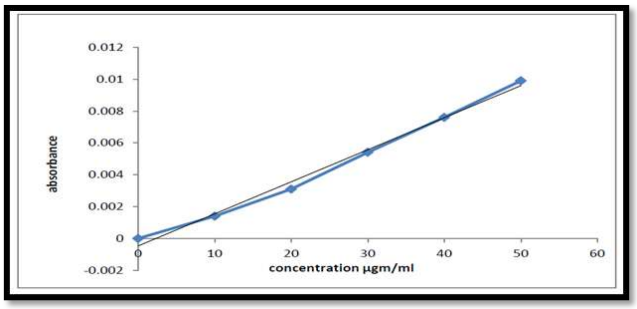

Fig. Calibration curve SADE in0.1 N HCl

Calibration curve of SADE in phosphate buffer pH 7.4: The absorbance values at different concentration obtained by double beam spectrophotometer (JascoV630) are given in Table. Using absorbance and concentration data the calibration curve was plotted as shown in Fig. The graph of absorbance Vs concentration was appeared to be linear in the concentration range of 10–50µg/ml at 314nm. Obey Beer-Lambert's law in the range of 10–50µg /ml.

Table: Calibration curve SADE in phosphate buffer pH 7.4

Concentration(µg/ml)	Absorbance at 341 nm
0	0
10	0.0075
20	0.0115
30	0.0174
40	0.0279
50	0.0356

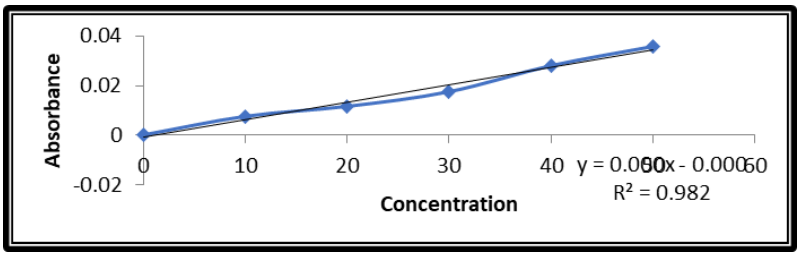

Fig. Calibration curve SADE in phosphate buffer pH 7.4

Calibration Curve of MUDE for Different Solvents

Calibration Curve in Methanol: The absorbance values at different concentration obtained by double beam spectrophotometer (JascoV630) are given in Table. Using absorbance and concentration data the calibration curve was plotted as shown in Fig. The graph of absorbance Vs concentration was appeared to be linear in the

concentration range of 10–50µg/ml at 250nm. Obey Beer-Lambert's law in the range of 10–50µg /ml.

Table: Calibration curve MUDE in methanol

Concentration(µg/ml)	Absorbance at 250 nm
0	0
10	0.1530
20	0.2565
30	0.3789
40	0.5098
50	0.6378

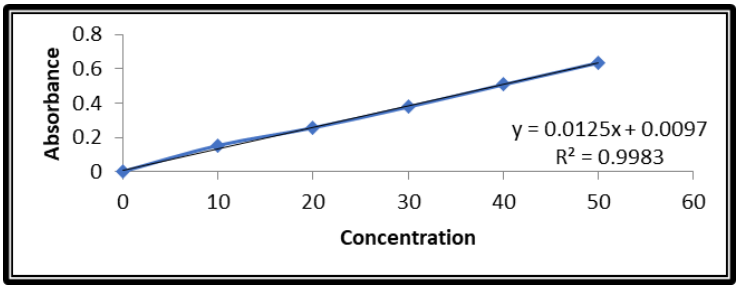

Fig. Calibration curve MUDE in methanol

Calibration Curve in Double Distilled Water

The absorbance values at different concentration obtained by double beam spectrophotometer (JascoV630) are given in Table. Using absorbance and concentration data the calibration curve was plotted as shown in Fig. The graph of absorbance Vs concentration was appeared to be linear in the concentration range of 10–50µg/ml at 250nm. Obey Beer-Lambert's law in the range of 10–50µg /ml.

Table: Calibration curve MUDE in double distilled water

Concentration(µg/ml)	Absorbance at 250 nm
0	0
10	0.1572
20	0.2649
30	0.3836
40	0.5244
50	0.6543

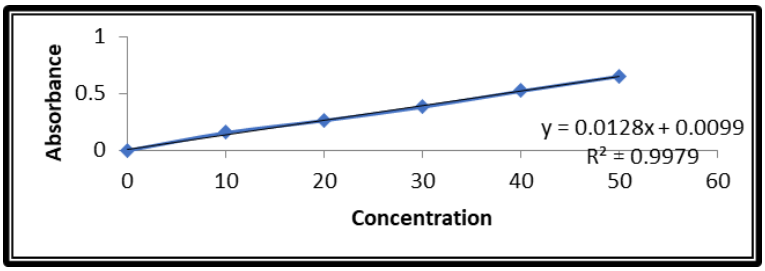

Fig. Calibration curve MUDE in double distilled water

Calibration Curve in 0.1N HCl

The absorbance values at different concentration obtained by double beam spectrophotometer (JascoV630) are given in Table. Using absorbance and concentration data the calibration curve was plotted as shown in Fig. The graph of absorbance Vs concentration was appeared to be linear in the concentration range of 10–50µg/ml at 250nm. Obey Beer-Lambert's law in the range of 10–50µg /ml.

Table: Calibration curve MUDE in 0.1N HCl

Concentration(µg/ml)	Absorbance at 250 nm
0	0
10	0.0434
20	0.0698
30	0.0857
40	0.0987
50	0.1380

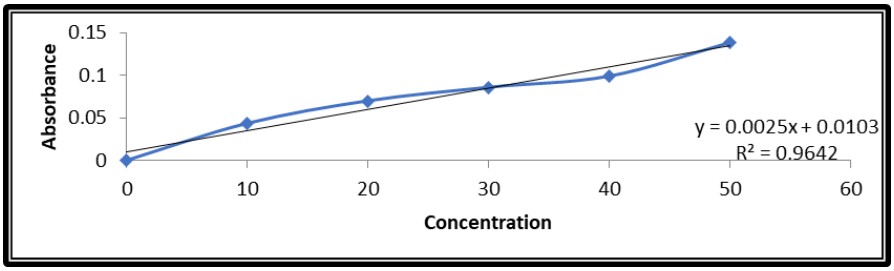

Fig. Calibration curve MUDE in 0.1N HCl

Calibration curve in phosphate buffer pH 7.4: The absorbance values at different concentration obtained by double beam spectrophotometer (JascoV630) are given in Table. Using absorbance and concentration data the calibration curve was plotted as

shown in Fig. The graph of absorbance Vs concentration was appeared to be linear in the concentration range of 10–50µg/ml at 250nm. Obey Beer-Lambert's law in the range of 10–50µg /ml.

Table: Calibration curve MUDE in phosphate buffer pH 7.4

Concentration(µg/ml)	Absorbance at 250 nm
0	0
10	0.1054
20	0.2549
30	0.4834
40	0.6719
50	0.8798

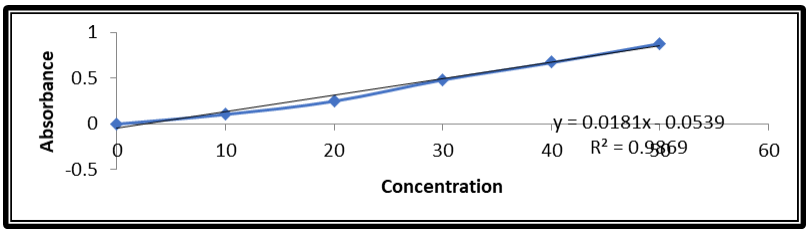

Fig. Calibration curve MUDE in phosphate buffer pH 7.4

Statistical data for analysis of SADE and calibration curve in various solvents

Table: various constants for calibration curve

Name of solvent	Slope	Intercept	Correlation coefficient
Methanol	0.000	0.003	0.982
Double distilled water	8.571	13.33	0.964
0.1 N HCl	0.012	0.005	0.982
Phosphate buffer pH 7.4	0.011	0.003	0.972

Statistical data for analysis of MUDE and calibration curve in various solvents

Table: various constants for calibration curve

Name of solvent	Slope	Intercept	Correlation coefficient
Methanol	0.000	0.003	0.982
Double distilled water	8.571	13.33	0.964
0.1 N HCl	0.012	0.005	0.982
Phosphate buffer pH 7.4	0.011	0.003	0.972

Preformulation Studies

- **Melting point:** Melting point of SADE was determined by capillary method which was found to be in the range of 132-135°C.
  Melting point of MUDE was determined by capillary method which was found to be in the range of 138-140°C.
- **Solubility Studies**

Table: Solubility of SADE and MUDE in different solvent

Name of solvent	Type of solubility
Methanol	Soluble
Water	Soluble
Ethanol	Very slightly soluble
Chloroform	Slightly soluble
0.1 N HCl	Soluble
Phosphate buffer pH 7.4	Soluble

SADE and MUDE were found to be soluble in Methanol, 0.1 N HCl, Phosphate buffer pH 7.4 and water, slightly soluble chloroform and it was very slightly soluble in ethanol.

Estimation of iron from SADE and MUDE

- **Acid Digestion/Atomic Absorption Method**

Table: Concentration of Fe (%) in SADE and MUDE

Sr. No.	Sample	Concentration of Fe (mg/100mg)
1	Sonchus asper dry extract	8.4
2	Memecylon umbellatum dry extract	2.6

- **Spectrophotometric Method**

Table: Concentration of Fe (%) in SADE and MUDE

Sr. No.	Sample	Concentration of Fe (mg/100mg)
1	Sonchus asper dry extract	8.5
2	Memecylon umbellatum dry extract	2.5

Formulation Design: Three batches of chewable tablets (A–C) were prepared by direct compression. It was observed that a decrease in HPC increased the disintegration time.

Evaluation of Granules: All test parameters were within BP limits, indicating good flow properties. Compressibility index (13–15%), Hausner's ratio (<1.25), and angle of repose (28°–31°) confirmed suitability for tablet formulation.

Table: Data for evaluation of granules

Batch code	Bulk density (gm/cm$^{3)}$	Tapped density (gm/cm$^{3)}$
A	0.453 ±0.035	0.538 ±0.034
B	0.436 ±0.045	0.529 ±0.041
C	0.409 ±0.024	0.503 ±0.021

(All readings are average ± SD, n=3)

Table: Data for evaluation of granules

Batch code	Angle of repose	Compressibility index	Hausner's ratio
A	28.34±1.2	13.21±0.65	1.15±0.023
B	29.65±1.3	15.45±0.98	1.10±0.014
C	30.85±1.4	14.34±0.87	1.04±0.032

Evaluation of Chewable Tablets: Uniform diameter ensures uniform swallowing. The results of weight variation, thickness, diameter, hardness, friability, and disintegration are presented in tables. The hardness of tablets ranged from 3.2–3.6 kg/cm², indicating good mechanical strength. Friability was below 1% for all formulations, confirming good mechanical resistance.

Table: Data for evaluation of formulations

Batch code	Hardness (Kg/cm^2)	Diameter (mm)	Thickness (mm)
A	3.2±0.17	11.66±0.1	5.05±0.2
B	3.6±0.15	11.67±0.3	5.06±0.1
C	3.5±0.13	11.63±0.5	5.15±0.3

All readings are average ± SD (n=3)

All the selected formulated tablets had acceptable friability as none of the tested formulae had percentage loss in tablet weights that exceed 1%, also; no tablet was cracked, split or broken in either formula. Since all the prepared formulae met the

standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packaging and shipment.

Table: Data for evaluation of formulations

Batch code	Weight variation(mg)	Friability (%)	Disintegrationtime (Sec)
A	500.2±0.40	0.99±0.03	54±0.2
B	499.8±0.20	0.89±0.02	68±0.3
C	500±0.30	0.98±0.03	73±0.2

All readings are average ± SD (n=3)

In vitro dissolution study

Dissolution medium: 900ml of methanol

Speed of Paddle: 50 RPM. Temperature of dissolution medium: 37ºC ± 0.5ºC.

Procedure: In-vitro dissolution study was performed using USP II (paddle) apparatus with methanol (900 ml) as dissolution medium maintained at 37±0.5°C and stirred at 50 rpm. Samples (5 ml) were withdrawn at intervals up to 120 minutes and replaced with fresh medium. The samples were filtered,diluted,andtreated with hydroxylamine hydrochloride and o-phenanthroline to form a colored complex. Absorbance was measured using a UV-visible spectrophotometer.

Table: Parameters for dissolution of chewable tablets of SADE and MUDE

Sr. No	Parameter	Specifications
1	Dissolution medium	900 ml methanol
2	Temperature	37ºC±0.5ºC
3	Rotation speed	50 rpm
4	Volume withdrawn	5 ml every 2 minutes
5	max	341 nm
6	Dilution factor	5 ml
7	Tablet taken	1 tab (known drug content)

Table: In-vitro release of tablet formulation in methanol

Time (min)	A	B	C
0	0	0	0
10	81±0.90	70±0.85	60±0.98
20	88±0.70	78±0.98	70±0.82
30	94±0.87	80±0.80	80±0.90
45	98±0.95	85±0.87	84±0.78

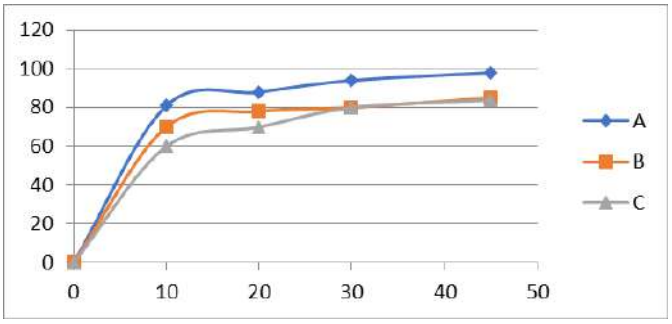

Fig. Comparision of time Vs drug release of three batches

From the above dissolution profile of A, B, and C, the maximum drug release was shown by (Batch) A and that was found to be 98% while other batches show minimum drug release.

Characterization of optimized formulation.

Estimation of iron from optimized formulation.

- **Acid Digestion/Atomic Absorption Method**

Table: Concentration of Fe (%) in SADE and MUDE

Sr. No.	Sample	Concentration of Fe (mg%)
1	Sonchus asper dry extract	8.5
2	Memecylon umbellatum dry extract	2.3

- **Spectrophotometric Method**

Table: Concentration of Fe (%) in SADE and MUDE

Sr. No.	Sample	Concentration of Fe (mg%)
1	Sonchus asper dry extract	8.5
2	Memecylon umbellatum dry extract	2.3

Stability Study: The effect of aging on hardness, disintegration time, and dissolution profile of SADE and MUDE tablets was evaluated by storing them at 25°C/75% RH for 1 month. Measurements were taken after 10, 20, and 30 days. Results showed no significant change in hardness (fresh: 3.2 kg/cm²; aged: 3.4–3.5 kg/cm²) and only slight increase in disintegration time (fresh: 54 sec; aged: 58–64 sec). Dissolution profiles remained nearly similar. Overall, aging had no significant effect, and the tablets were stable for up to 30 days.

Conclusion

Phytochemical screening confirmed the presence of iron in both natural sources, with Sonchus asper showing higher iron content than Memecylon umbellatum by both methods. Wet granulation using starch mucilage as a binder was found suitable

based on good flow properties. Among the formulations, Formulation A was optimized due to its lower disintegration time and higher drug release, while a decrease in HPC increased disintegration time. Each tablet contained an average of 10 ± 0.2 mg of iron, and the presence of ascorbic acid in the extract may enhance the solubility of non-heme iron. The study confirms that SA and MU are promising natural sources for preventing iron deficiency. The prepared tablets were stable for at least one month, although further studies are required to evaluate the bioavailability of the optimized formulation.

Sr. No.	Abbreviations	Full Form
1	UV	Ultra-Violet Spectroscopy
2	SA	Sonchus Asper
3	MU	Memecylon Umbellatum
4	HPC	Hydroxypropyl Cellulose
5	MS	Magnesium Stearate
6	SADE	Sonchus Asper Dry Extract
7	MUDE	Memecylon Umbellatum Dry Extract
8	HCl	Hydrochloric acid
9	ml	Milliliter
10	BP	British Pharmacopeia
11	IP	Indian Pharmacopeia
12	Hrs	Hours
13	ICH	International Conference of Harmonisation

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