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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).

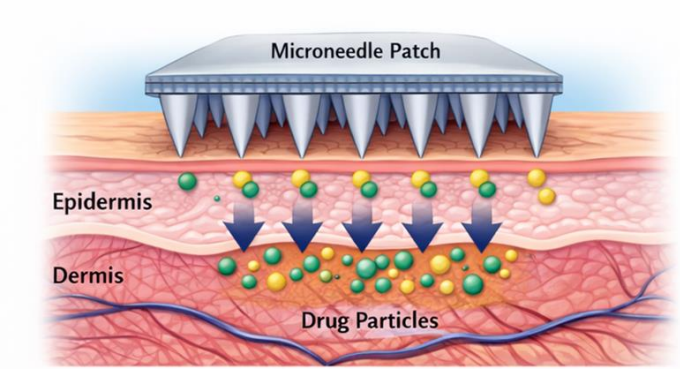

Figure 1. Schematic of a microneedle array penetrating the skin to deliver therapeutic agents.

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.

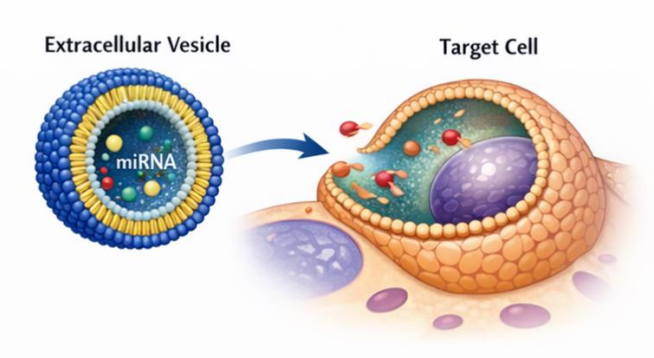

Figure 2. Extracellular vesicle encapsulating miRNA delivered to a target cell.

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).

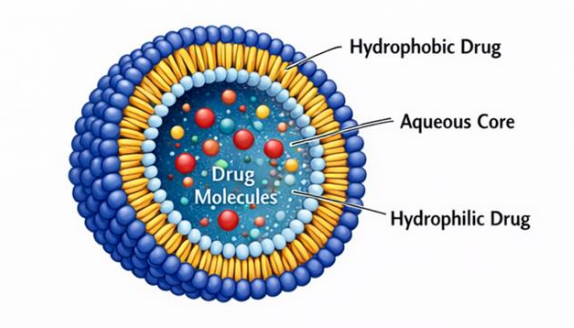

Figure 3: Liposomal Drug Delivery System

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.

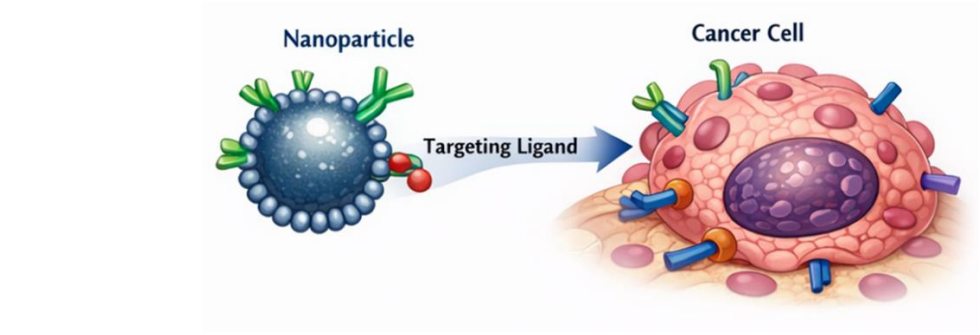

Figure 4. Nano-carrier with targeting ligand binding to cell surface receptors.

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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