

SYNERGIZING LIPID-BASED NANOPARTICLES, MICROROBOTICS, AND PLANT-DERIVED AGENTS FOR PRECISION DRUG TARGETING

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ABSTRACT

Targeted drug delivery systems are transforming contemporary therapy with more precision, efficacy, and safety. Recent developments for the past few years are discussed here with focus on lipid-based nanospheres, microrobotic platforms, and plant-derived molecules for more efficient, targeted therapeutic treatment. Liposomal and vesicular nanocarriers provide controlled release of the drug and biocompatibility with living systems, whereas structural innovations enhance stability and efficacy of the payload. Target-directed codeable by being polymer-based, lipid nanoparticles respond to biologic signals like pH and availability of enzymes. PEGylation and pH-sensitive carriers increase tumor-targeted delivery coupled with decreased overall toxicity. Magnetic microrobots and microdevices offer a novel paradigm of active navigation and localization, especially deep within tissues. Effervescent tablets and proniosomal systems provide greater oral bioavailability

and patient compliance, and incorporation of phytomedicinal drugs such as Tribulus terrestris demonstrates successful merging of traditional medicine and nanocarrier systems. Natural extracellular vesicles have been engineered as biocompatible nontoxic drug delivery systems based on their intrinsic properties and targeted delivery capability to cells selectively. Reproducibility, regulatory approval, and long-term safety still pose issues with translation even in this regard. The review presents an integrated view of these heterogeneous yet interconnected strategies, invoking the impetus of interdisciplinarity to create clinically

applicable smart delivery systems. Synergistic application of lipid-based nanocarriers, microrobots, and phytochemicals is a landmark advance towards efficient, tailored, and minimally invasive drugs.

KEYWORDS

- Lipid Nanoparticles
- Microrobotics
- Targeted Drug Delivery
- Herbal Medicine
- Extracellular Vesicles

1. Overview of Precision Drug Delivery Paradigms

The science of drug delivery has completely changed with the advent of precision medicine, which seeks to deliver therapeutic agents to locations of disease while minimizing toxicity to the patient as a whole. With this new mindset, sophisticated drug delivery systems can be developed to optimize pharmacokinetics and pharmacodynamics from a biological, chemical, and engineering perspective, so that the therapeutic agent can be delivered to intended sites of action exclusively and not to healthy sites.^[1] There are many examples of the exponential leap in the field of drug delivery, which is neither different levels of pill development nor injections, but which are now controlled-by-signal delivery systems. Nanotechnology has emerged as a leading technology platform, with multiple options for flexible delivery systems, such as liposomes, nanoparticles and vesicular carriers, which are designed to respond to signals from physiology. These drug delivery systems can not only efficiently encapsulate a drug but also stabilize it from degradation, and present consistent release profiles to simplify patient doses.^[2] With advances in ligand targeting and surface decoration, nanocarriers can now provide a greater specificity to tumor microenvironments and sites of inflammation. Moreover, initial studies of cancer nanotechnology suggested the promise of benefits as well as obstacles in the application of nanosystems from laboratory to bedside. Although nanoscale carriers could provide heightened therapeutic concentration within tumors because of the enhanced permeability and retention (EPR) effect, heterogeneous tumor blood vessel architectures and biological barriers still existed.^[3] These eye-opening observations led to the development of adaptive delivery strategies in the modern treatment strategies we now see. As a result, the drug delivery space has shifted from an individualized effort to the collaborative effort of advancing treatment across nanoscience, biomedical

engineering, and molecular biology to optimize the maximum treatment performance and patient impact.

2. Structural Principles of Lipid-Based Nanoparticles

Lipid-based nanoparticles, particularly liposomes and similar vesicular systems, play a pivotal role in contemporary drug delivery thanks to their biocompatibility, structural adaptability, and ability to encapsulate hydrophilic and lipophilic medications. Central to these systems is the amphiphilic bilayer structure, which replicates natural biological membranes and facilitates selective engagement with cellular elements.^[4] The lipid makeup—comprising phospholipids, cholesterol, and surface modifiers—crucially influences their size, surface charge, fluidity, and drug release rates. The adaptable nature of liposome design permits customized delivery profiles by modifying factors like bilayer stiffness, lamellarity (uni- or multi-lamellar vesicles), and the addition of targeting ligands. These design features improve circulation duration, cellular absorption, and intracellular movement, maximizing therapeutic effects on targeted conditions like cancer, infections, and inflammation.^[5] Recent advancements in lipid nanoparticle (LNP) formulations—such as PEGylation, materials that respond to stimuli, and surface modifications—have broadened the possibilities of these systems. Strategies for encapsulation, particularly regarding nucleic acids and chemotherapeutics, are consistently advancing to overcome issues such as stability in biological fluids and endosomal release.^[6] These developments establish lipid-based nanocarriers as prominent systems for the future of drug delivery, encompassing gene editing technologies and vaccine administration.

3. Engineering of Vesicular Systems for Controlled Release

Controlled release of pharmaceuticals using vesicular drug delivery systems, especially liposomes, plays an important role in precision pharmacotherapy. These nano- and micro-vesicles are constructed to release therapeutic agents over longer periods of time or directed at a specific target site, improving their efficacy while minimizing the risk of systemic toxicity. The mechanism behind this will largely depend on the physicochemical properties of the vesicle's lipid bilayer, as well as the physiochemical way in which the drug is encapsulated, and the environmental interaction of the vesicle.^[7] Liposomal formulations are built on a basis of molecular engineering, in which the lipids are assembled with a variety of structures, surface charges, bilayer fluidity, to meet specific release kinetics. For example, including cholesterol in liposomes stabilizes the bilayer to minimize leakage and provide a

more predictable release profile.^[8] In the same manner, the amount of PEGylation can influence the length of time in circulation and can help reduce premature clearance by the mononuclear phagocyte system. Recent implementation of lipid compositions contain pH-sensitive lipids or enzyme cleavable lipids, which allows for liposomes to be primed to release upon exposure of the liposome to an acidic use environment like the tumor microenvironment, or an intracellular compartment. The use of stimuli-responsive lipids is an important step toward enhanced pharmacologically active delivery through advanced control of the bioavailability and spatiotemporal delivery of the therapeutic agent.^[9] Additionally, targeted vesicles that use antigen/antibody or peptide functionalization have been found to improve site specificity in use with oncology and inflammatory diseases. In the end, the engineering of vesicular systems has increased from a static, passive carrier to an intelligent nanoplatform which can respond to biological signals, a powerful application in personalized medicine.

4. Programmable Lipid Nanoparticles and Targeting Strategies

Programmable lipid nanoparticles (PLNs) are a novel platform for targeted drug delivery that can also harness lipid stability, and also have programmable responsive behaviors. These systems are designed to respond to a physiological condition like pH, temperature, or enzyme concentrations to improve site-specific drug release and reduce off-target actions.^[10] Incorporating polymeric materials into lipid nanoparticle designs allows researchers to fine-tune other desirable properties, such as biodegradability, release kinetics, or cellular uptake. Zielińska *et al.* describe hybrid polymer-lipid systems that can help researchers achieve a tighter control of pharmacokinetics and pharmacodynamics of the encapsulated therapeutics, particularly in cancer and neurodegenerative disease treatment models.^[10] Liu *et al.* proposed a four-domain model of programmable lipid nanoparticles which describes a core structure organized into functional compartments that can provide payload protection, specific targeting, environmental responsiveness, and controlled release.^[11] The modularity that comes with combining the four-domain model, the platform's inherent properties, and evolution of PLNs, gives PLNs greater flexibility in meeting acute clinical needs for RNA delivery, immune modulation, or combination therapies. Active targeting is also possible by enabling the outer layer with ligands or antibodies therefore preferentially accumulating the drug-delivery system to disease sites such as tumors or inflamed regions. PLNs combine lipidability with polymeric precision, giving PLNs an intuitive platform for next generation

drug delivery systems. Programmability can ensure more efficacious pharmacology, less systemic toxicity, and possibly real-time response.

5. pH-Responsive and PEGylated Nanocarriers for Tumor Delivery

Due to the lower extracellular pH and leaky vasculature that are often present in tumor microenvironments, they provide a unique opportunity to develop stimuli-responsive drug delivery systems. One of these systems is pH-responsive and PEGylated nanocarriers which can greatly improve the release of chemotherapeutics within acidic tumor tissues.^[12] Song et al. developed Schiff base-linked PEGylated doxorubicin prodrugs which were capable of self-forming nanoparticles. The nanoparticles are stable in the physiological pH range but rapidly disassemble to release the drug in acidic environments. This allows for drug release specifically at the tumor site.^[12] This method of drug delivering will minimize premature leakage during circulation while maximizing therapeutic payload at the desired tumor target. Zhang et al. also reported a dextran–doxorubicin prodrug system that degraded under mildly acidic conditions. The resultant pH-sensitive nanoparticles had enhanced cellular uptake and associated cytotoxicity in tumor cells in part because these particles degraded under endosomal and extracellular tumor acidity.^[13] Customizing responsiveness of drug carriers dramatically enhances intracellular delivery and the effectiveness of anticancer agents. Jain and Stylianopoulos reaffirmed the need for and specific usefulness of these responsive systems by discussing the issues with delivering nanomedicines to solid tumors. They specifically addressed PEGylation—surface-modifying particles with polyethylene glycol—that has been found to not only improve the circulation time of molecules by evading the mononuclear phagocyte system, but also increases the enhanced permeability and retention (EPR) effect.^[14] In other words, PEGylation plays a dual role in targeting by enhancing passive accumulation and aiding controlled intracellular releasing. pH-responsive and PEGylated nanocarrier systems represent a potent synergy that increases specificity, stability, and therapeutic effectiveness for tumor-targeted drug delivery.

6. Magnetic Microrobots: Active Navigation and Localized Therapy

Microrobots that possess magnetic propulsion represent a novel means to provide precision medicine - microrobots can provide active propulsion to enable the microrobot to move inside the body with little resistance. Microrobots can move more accurately in difficult-to-reach anatomy than passive nanocarriers or other systems that are manipulated externally with magnetic fields. For example, Landers et al. demonstrated microrobots capable of

clinically-relevant locomotion in both vascular and tissue environments. These microrobots facilitated drug delivery by carrying a therapeutic payload and are able to release that payload precisely at the delivery site without unnecessary side effects on the surrounding normal tissue. This particular study demonstrated that the microrobots are biocompatible, can respond to external stimuli, and can be controlled with real-time precision - all positive qualities for a clinical therapeutic device. The microrobots were controlled using an MRI-compatible magnetic system, which further supports their eventual use as a therapeutic delivery agent in treating cancer and vascular disease. Collectively, the utility of microrobots represents an improved precision delivery of therapeutics with minimal off-target cytotoxicity associated with many therapies.^[15]

7. Effervescent and Proniosomal Systems for Enhanced Bioavailability

Drug delivery systems with the use of novel oral drug forms, including effervescent and proniosomal drug forms, are attracting greater interest owing to the possibility of enhancing drug solubility, permeation, and patient compliance. Proniosomes are free-flowing, dry granules that, upon rehydration, convert into niosomes which have been proven to increase lipophilic as well as hydrophilic drug stability and bioavailability. Sengar et al. emphasized the structural versatility and capacity of proniosomes to encapsulate a range of drugs and resist degradation in the gastrointestinal tract.^[16] Furthermore, effervescent systems are capable of quick disintegration and drug dispersion upon exposure to water or gastric fluids. Effervescent systems are founded on acid-base chemistry that favors the production of carbon dioxide upon meeting water, aiding dissolution, and favoring quicker drug release. Sengar et al. reported that effervescent tablets represent an ideal form for patients with dysphagia and cases in which a quick onset of action is desirable.^[17] The combination of these systems then offers an innovative solution for improving the oral delivery of poorly soluble agents.

8. Integrating Plant-Derived Agents in Nanocarrier Platforms

The addition of herbal medicine along with nanocarriers represents a new frontier in targeted therapies, particularly for conditions like urolithiasis. Many plant-derived compounds, such as those derived from the herb *Tribulus terrestris*, exhibit therapeutic properties, including diuretic, anti-inflammatory, and antioxidant properties. Sengar et al. demonstrated a more effective way of delivering these bioactive compounds by putting the actives into nano-formulations like liposomes and proniosomes to improve their bioavailability and therapeutic index.^[18]

Encapsulation of herbal extracts will also allow the new formulations to evade some of the pharmacokinetic limitations often observed with phytochemicals (e.g. poor solubility, rapid metabolism). This shift in treatment methodology integrates nanoparticles, naturally sourced actives and bioavailability within one treatment regimen, which is especially relevant around personalized medicine and sustainable therapies.^[18]

9. Extracellular Vesicles as Natural Delivery Vehicles

Extracellular vesicles (EVs) appear naturally occurring carriers with great promise for therapeutic delivery. EVs are released by nearly all cell types, serve as intercellular communicators and can carry proteins, lipids and nucleic acids. Their biocompatibility due to their naturally occurring nature and the ability to cross biological barriers make them attractive carriers for drug delivery. Yáñez-Mó *et al.* provided an overview of the basic functions of EVs within a physiological framework, including immune-modulation, tissue repair, and signaling during pathological events, which could all be used as a rationale for controlled therapeutic delivery.^[19] Unlike synthetic nanoparticles, a major advantage of EVs is their lack of recognition and clearance by the immune system. EVs includes a phospholipid bilayer like conventional liposomes; however, unlike conventional liposomes that attract plasma proteins which rapidly leads to clearance, EVs can be circulated longer due to their natural composition. Chonn and colleagues showed that synthetic liposomes typically have a high affinity for blood proteins leading to increased uptake by the mononuclear phagocyte system—a phenomenon that does not apply to EVs.^[20] In addition, vesicle-based systems were clinically evaluated by Puglia *et al.*, who illustrated successful topical delivery of anti-inflammatory agents using vesicular formulation. Their results confirmed improved skin penetration and also supported the use of vesicular systems for local therapy.^[21]

10. Safety, Translational Challenges, and Clinical Outlook

The shift towards using lipid-based nanocarriers, microrobotic systems, and plant-derived agents in clinical protocols will have to be assessed for safety, scalability, and long-term efficacy. Liposomes were considered the first class of nanoparticle nanocarriers that have been investigated for clinical translation and were largely promoted by Gregoriadis and Florence for their low toxicity, applicability for encapsulation and delivery of both hydrophobic and hydrophilic drugs.^[22] There continues to be issues of stability in biological fluids, and whether they confer potential immunogenicity. Current day platforms like mesoporous silica nanoparticles (MSNs) are presently being investigated for clinical

translation where they have transportable porosity and transportable surface functionality. Mann *et al.* have specifically cited MSNs' targeted delivery capacity for investigating a targeted approach for cancer therapy, in particular colorectal cancer.^[23] Nevertheless, there were some mechanistic apprehensions regarding MSNs presenting some potential toxicity from body retention and biodegradability; this should be explored in greater detail before transferring to the clinic. The observations highlight the need for sufficient preclinical studies and pharmacokinetic studies over a longer timeframe. On a broader scale, nanotechnology coupled with oncology has made great strides in diagnostic accuracy and treatment precision. Nie *et al.* point out the increased particle accumulation in tumor tissues caused by the enhanced permeability and retention (EPR) effect when using nanocarriers, but reproducibility in human tumors fails due to the differences in tumor microenvironment and immune response.^[24] Sengar points out that the need to optimize formulations and design formulations that manufacture good practices (GMP) is considerable and although will satisfy regulatory bodies, will not impact therapeutic effectiveness.^[25] The future of these platforms are nestled in innovation without losing translational feasibility, reliability, and safety will ultimately realize all the potential in these technologies to realize personalized medicine.

CONCLUSION

The dynamic world of precision drug delivery necessitates a comprehensive approach that fuses biological functioning with engineered technologies. In this article, we discussed the recent advances in smart drug delivery systems starting from lipid-based nanoparticles and vesicular systems that offer biocompatibility and sustained release. Additionally, it was shown that programmable and PEGylated nanocarriers are effective under pH-responsive conditions, especially for tumor targeting. The introduction of magnetic microrobots offered active control with spatial precision to overcome the challenge of drug delivery to difficult-to-reach tissue. Effervescent and proniosomal formulations will also increase bioavailability and patient compliance. Furthermore, *Tribulus terrestris*, as a herbal agent, signifies the promise of phytomedicine in novel formulations of products. Next, extracellular vesicles emerged as an innovative natural transporters for biological drug delivery due to their inherent targeting and safety profiles. Although these technologies are promising, the road to translation into patients will have their own hurdles including biocompatibility, long term toxicity, reproducibility and delivery. This review highlighted that continued collaboration among disciplines is important in the design, evaluation and regulatory processes.

Nevertheless, the promise of lipid carriers, microrobots and bioactive botanicals represents a transformative path towards achieving site specific, patient selected and compatible therapies.

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