International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 **ijppr.humanjournals.com** ISSN: 2349-7203

Exploring the Frontiers of Drug Delivery: New Approaches and Emerging Technologies

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Received: 2024-10-11 Revised: 2024-10-17 Accepted: 2024-10-22

ABSTRACT

The landscape of drug delivery has evolved significantly over the past few decades, driven by the need for more effective, targeted, and controlled therapeutic strategies. Novel drug delivery systems (NDDS) are at the forefront of this revolution, offering solutions to the limitations of traditional drug delivery methods, such as poor bioavailability, unwanted side effects, and lack of tissue specificity. This review aims to explore the latest advancements in drug delivery technologies, focusing on emerging approaches that leverage nanotechnology, biocompatible carriers, and cutting-edge engineering techniques. We discuss innovations in nanocarriers, such as liposomes, nanoparticles, niosomes, and erythrocyte carriers, and their potential applications in precision medicine. Additionally, we examine the role of biomaterials, excipients, and genetic engineering in improving drug stability, bioavailability, and targeted drug release. This review also addresses the challenges and opportunities in translating these technologies from research to clinical practice.

Keywords: NDDS, nanoparticles, liposomes, niosomes, erythrocyte carriers.

INTRODUCTION:

Various methods have been employed to enhance the solubility, sustainability, bioavailability, and gastrointestinal permeability of drugs. With the advent of new drug carriers and delivery techniques, nanocarriers have garnered significant attention (Martinelli C et al., 2019), (Wolfram J et al., 2015), (Rizvi SA et al., 2018), (Baeza A et al., 2017). One solution to these challenges is encapsulating natural plant metabolites in biodegradable and biocompatible nanoparticles. Additionally, modifying the key attributes of nanocarriers—such as their shapes (spherical, rod-like, or cubic), sizes (small, medium, or large), compositions (organic, inorganic, or hybrid), and surface properties (charge, functional groups, PEGylation, or attachment of targeting ligands)—is believed to play a crucial role in optimizing their physiochemical properties (Bao et al., 2004).

Nanotechnology has revolutionized the field of drug delivery by enabling the creation of highly efficient, targeted, and controlled delivery systems. Nanocarriers, including nanoparticles, liposomes, and dendrimers, can be engineered to encapsulate drugs and deliver them directly to the target site, improving therapeutic outcomes while minimizing side effects (Roduner E, 2006). The use of nanocarriers in drug delivery aims to treat a condition as efficiently as possible while minimizing adverse effects and unwanted outcomes. This innovative drug delivery system represents a groundbreaking approach that overcomes the limitations of conventional drug delivery methods. Although Ayurvedic knowledge has long been abundant in our country, its full potential has only recently begun to be realized. While patients receive herbal medicine, the effectiveness of the treatment is often diminished by the traditional and outdated drug delivery systems (Attia MF et al., 2016). Modern drug delivery technology holds the potential to enhance the therapeutic effects of various plants and herbal components while reducing their side effects. This concept forms the foundation for applying innovative drug delivery methods in herbal remedies (Dou Y et al., 2017).

Before scientists began developing artificial treatments for every illness, and before pharmaceutical companies turned healthcare into the multibillion-dollar industry it is today, medicine had much humbler origins. For centuries, plants were humanity's primary source of chemical compounds, forming the basis for nearly all treatments. Today, we are witnessing a global "renaissance" in herbal medicine, as more people turn to plant-based remedies over conventional pharmaceuticals to treat various conditions. The way a medication is administered can significantly influence its effectiveness (Chetprayoon P et al., 2015). Some drugs have an optimal concentration range where they provide the greatest therapeutic benefit; dosages outside this range can either be harmful or ineffective. Meanwhile, the slow progress in effectively treating serious diseases has highlighted the growing need for a

multidisciplinary approach to delivering medicines directly to target tissues. This has inspired the development of new strategies for controlling pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, and biorecognition (Chhour P et al., 2016).

These innovative approaches, often referred to as novel drug delivery systems (NDDS), are built on multidisciplinary methods that integrate polymer science. Many drug delivery and targeting systems are currently being developed to reduce drug loss and degradation, minimize side effects, enhance drug bioavailability, and increase the concentration of the medication at the intended site of action. Drug carriers include soluble polymers, micelles, cells, cell ghosts, lipoproteins, liposomes, and microparticles made from biodegradable or insoluble natural and synthetic polymers. These carriers can be designed to degrade gradually, respond to external stimuli (such as changes in pH or temperature), or be targeted specifically to desired locations (Chandramouli S et al., 2015). Nanotechnology offers numerous advantages in the treatment of chronic human diseases by enabling precise drug targeting and delivery. Recently, there have been several significant applications of nanomedicine, including the use of chemotherapeutic drugs, biological agents, immunotherapeutic agents, and more, in the treatment of a wide range of diseases. These advancements allow for more effective therapies with potentially fewer side effects, as drugs can be delivered directly to the affected areas (Cai W et al., 2008). Nanoparticles are gaining attention for their ability to deliver drugs with high precision. Their small size allows for enhanced penetration into tissues and cellular uptake, making them ideal for treating localized diseases such as cancer, neurological disorders, and infections. Various carriers include:

1. Nanostructured Lipid Carrier (NLC):

Despite having more lipid matrix defects, the NLC is considered a second-generation lipid nanoparticle, derived from solid lipid nanoparticles (SLN). Its lipid composition consists of both solid and liquid lipids. While a wide range of liquid lipids, such as olive oil, mustard oil, castor oil, and cod liver oil, are commonly used, solid lipids like hydrogenated palm oil (HPO), glyceryl monostearate, stearic acid, and cetyl alcohol are also extensively employed. Methylosal is often used as a stabilizer in this system. Food-grade lipids, such as cocoa butter and olive oil, are effectively loaded into NLCs using the synthesis of 2Cardamom essential oil (CEO). CEO-loaded NLCs exhibit high loading capacity (>25%), compact size (90%), and strong physical and chemical stability. This innovation overcame the challenge of CEO's limited application in water-based food products. Currently, several advanced NLCs, such as those loaded with citral, zerumbone, and thymoquinone, are being developed as carriers to target anticancer activities. These drugs have shown significantly improved antitumor activity in leukemia and breast cancer cells, both *in vitro* and *in vivo* (Opez-Gracia R et al., 2015).

2. Nanocells:

The indiscriminate distribution and severe toxicity associated with systemic chemotherapy can be addressed through the encapsulation of chemotherapeutic agents in 400 nm nanocells, which are capable of packaging significant concentrations of drugs with varying charges, hydrophobicity, and solubility (Mac Diarmid JA et al., 2007). These nanocells can be targeted to cancer cells using bispecific antibodies that bind to specific receptors on the cancer cell membranes, triggering endocytosis, intracellular degradation, and subsequent drug release. Remarkably, the dosage of drugs delivered via nanocells is approximately 1,000 times lower than the dose of free drugs needed to achieve the same level of tumor regression. In preclinical studies, this approach has demonstrated significant inhibition of tumor growth and tumor regression in mouse xenograft models and lymphoma in dogs, even with the administration of extremely small amounts of both drug and antibody. The ability to drastically reduce dosage is crucial in minimizing systemic toxicity, making this a promising advancement in cancer therapy. Clinical trials are being planned to further evaluate this drug delivery method in humans.

3. Nanotubes:

While it has been possible to directly attach drug molecules to antibodies, doing so in large quantities tends to hinder the antibody's targeting ability due to the interference of chemical bonds with antibody activity. To address this limitation, various nanoparticles have been explored. For example, tumor-targeting single-walled carbon nanotubes (SWCNTs) have been synthesized by covalently attaching multiple copies of tumor-specific monoclonal antibodies (MAbs), radiation ion chelates, and fluorescent probes (McDevitt MR et al., 2007). A new class of anticancer compounds has also been developed that combines tumor-targeting antibodies with nanoparticles known as fullerenes (C60). This system can be loaded with multiple anticancer drug molecules, such as Taxol (Ashcroft JM et al., 2006). One example involves loading up to 40 fullerenes onto a single skin cancer antibody, ZME-108, to deliver drugs directly into melanoma cells. Certain binding sites on the antibody are hydrophobic, which attracts hydrophobic fullerenes, allowing multiple drug molecules to be loaded onto a single antibody in a spontaneous process without the need for covalent bonds. This avoids significantly altering the antibody's targeting ability. The key advantage of fullerene-based therapies compared to other targeted treatments is their ability to carry multiple drug payloads, such as Taxol in combination with other chemotherapeutic agents. Since cancer cells can develop resistance to drugs, delivering more than one type of drug simultaneously

may reduce the chance of the cancer escaping treatment. The first fullerene immuno-conjugates have been synthesized and characterized as a crucial step toward the development of fullerene-based immunotherapy.

4. Gold nanoparticles (GNPs):

Gold nanoparticles have demonstrated significant potential in photothermal therapy and targeted drug delivery due to their unique optical properties and biocompatibility. Gold nanoparticles (GNPs) have emerged as a significant type of nanomaterial, celebrated for their exceptional physicochemical properties that make them highly effective in medical applications. Their unique optical characteristics, coupled with their potential in photothermal and radiation therapy, have opened new avenues for the early diagnosis and treatment of cancer. GNP-based nanostructures are biocompatible, non-toxic, and offer a large surface area, allowing for modification with various substances such as polymers, antibodies, and even therapeutic agents. This versatility enables GNPs to be used in targeted drug delivery systems, where they can precisely transport pharmaceuticals to specific tissues, reducing harmful effects on healthy cells while increasing the drug's concentration at cancerous sites. This paper primarily focuses on the fundamental properties of GNPs and their applications in drug delivery (Daniel MC et al., 2004).

5. Nanomaterial formulation:

Nanomaterials have been successfully engineered to develop a new drug delivery system that addresses the issue of poor water solubility in many promising anticancer drugs, thereby enhancing their effectiveness. Typically, these poorly soluble drugs require the use of solvents to aid their absorption into cancer cells, but the solvents not only reduce the drug's potency but also introduce toxicity. Researchers from the University of California Los Angeles California Nanosystems Institute have pioneered a novel technique using silica-based nanoparticles to deliver the anticancer drug CPT and other water-insoluble drugs directly to cancer cells (Lu J et al., 2007). This approach involves incorporating the hydrophobic anticancer drug CPT into the pores of fluorescent mesoporous silica nanoparticles, which are then delivered into various human cancer cells to trigger cell death. The findings indicate that mesoporous silica nanoparticles could serve as an effective delivery vehicle for overcoming the solubility challenges associated with many anticancer drugs.

6. Liposomes:

spherical vesicles with one or more phospholipid bilayers, were first characterized in the mid-1960s. Today, they are an invaluable tool in various fields, including biology, chemistry, biophysics, mathematics, theoretical physics, colloid science, and biochemistry. Liposomes have been commercially available for many years, and a range of novel drug delivery technologies, including liposomes, are currently being tested in clinical trials (Rosenthal E et al., 2002). Liposomes represent cutting-edge technology for delivering active substances precisely where they are needed. Liposome technology has evolved from traditional vesicles to "second-generation liposomes," which are long-circulating vesicles created by modifying their size, charge, and lipid composition. Among the substances used to alter the surface of liposomes are glycolipids, which contribute to their enhanced functionality (Mazur F et al., 2017). Over the past 30 years, liposomes—tiny phospholipid vesicles with a bilayered membrane structure—have garnered significant attention as highly promising pharmacological carriers. The primary focus has remained on gene delivery and cancer therapy, though recent advancements in liposomal drug research have introduced novel experimental applications and clinically approved drugs. For this field to continue progressing, it is essential to identify and build on promising trends while recognizing the limitations of these approaches. Nanomedicine and nano-delivery systems, though relatively young, are rapidly evolving fields. These systems utilize nanoscale materials as diagnostic tools or to deliver therapeutic agents precisely to targeted locations in a controlled manner (Chang HI et al., 2012).

7. Niosomes:

In recent years, there has been a significant shift in the management of infectious diseases and vaccination methods. Advances in biotechnology and genetic engineering have led to the development of numerous biologicals targeted at specific diseases, but attention has also shifted to improving the delivery of these biologicals. Niosomes, which are vesicles composed of non-ionic surfactants, offer several advantages over liposomes. They are more stable, nontoxic, biodegradable and less expensive (Pardakhty A et al., 2007). Niosomes are versatile drug delivery systems, functioning as self-assembling vesicular nano-carriers formed by hydrating non-ionic surfactants, cholesterol or other amphiphilic compounds. These carriers can be utilized for various applications, including cutaneous drug delivery and brain-targeted therapy. Numerous research publications have explored the production methods and applications of niosomes in both the cosmetic and pharmaceutical industries. Compared to liposomes, niosomes offer several advantages, such as the ability to incorporate both hydrophilic and lipophilic materials. Additionally, they are more cost-effective to produce, easier to formulate, and offer enhanced stability, making them a promising alternative to liposomes (Moser P et al., 1989).

8. Microspheres:

Multiparticulate drug delivery systems, commonly known as microspheres, are engineered to deliver drugs to specific sites at controlled rates, allowing for delayed or sustained release to improve bioavailability and stability. These systems often include protective materials like polymeric wax and can be made from synthetic, natural, or semi-synthetic polymers. Typically consisting of proteins or synthetic polymers, microspheres are free-flowing powders with particle sizes between 1 and 1000 micrometers (Chaudhari A et al., 2010). The various techniques available for forming microspheres offer numerous possibilities for controlling drug release, which in turn enhances the therapeutic effectiveness of medications. Recent developments have focused on improving in vitro release testing of microspheres using methods such as USP apparatus IV, sample and separate techniques, and dialysis membrane sacs. Among these, USP apparatus IV has become the preferred method for quality control due to its ability to accelerate testing. By using real-time and accelerated release data, in vitro-in vivo correlations (IVIVC) have been developed, reducing the need for extensive in vivo performance testing. Research has also examined storage stability to assess how different environmental conditions affect microsphere quality over time. Alongside advancements in characterization techniques, such as evaluating drug content, particle size, and thermal properties, new tests like the in vitro wash-off test and the floating test have been introduced to further enhance microsphere evaluation (Shanthi NS et al., 2010).

9. Hydrogels:

Hydrogel nanoparticles are based on proprietary technology that utilizes hydrophobic polysaccharides for the encapsulation and delivery of drugs, therapeutic proteins, or vaccine antigens. A promising example is a system that uses cholesterol pullulan, where four cholesterol molecules form a self-aggregating hydrophobic core surrounded by pullulan. These cholesterol nanoparticles stabilize entrapped proteins by creating a hybrid complex, which enhances immune system stimulation and facilitates uptake by dendritic cells. In addition, larger hydrogels can encapsulate and release monoclonal antibodies. Curcumin, a compound found in turmeric, is known for its anti-cancer properties but has been limited in clinical use due to poor solubility and low systemic bioavailability. This issue has been addressed by encapsulating curcumin in a polymeric nanoparticle, creating "nanocurcumin" (Bisht S et al., 2007). The mechanism of action of nanocurcumin in pancreatic cancer cells is similar to that of free curcumin, inducing apoptosis, blocking nuclear factor kappa B (NFκB) activation, and downregulating pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α. Nanocurcumin improves the solubility and dispersion of curcumin, offering a way to expand its clinical use. Further studies on nanocurcumin in preclinical in vivo models are needed to explore its potential for treating cancer and other diseases.

10. Polymersomes:

Polymersomes, which are hollow shell nanoparticles, possess unique properties that enable the delivery of different drugs. The loading, delivery, and cytosolic uptake of drug combinations from degradable polymersomes take advantage of the thick membranes of these block copolymer vesicles, their aqueous cores, and their ability to release drugs in a pH-triggered manner within endolysosomes. In the acidic environment of tumor cell endosomes, polymersomes break down to release their drug payloads. Unlike cell membranes and liposomes, which consist of a double layer of phospholipids, polymersomes are made of two layers of synthetic polymers. These polymers are much larger than individual phospholipids but share similar chemical properties. Polymersomes have been used to encapsulate both paclitaxel and doxorubicin (DOX) for passive delivery to tumors in mice (Ahmed F et al., 2006). The large polymers in the polymersome structure allow paclitaxel, which is water-insoluble, to be embedded within the shell, while DOX, which is water-soluble, remains in the polymersome's interior until it degrades. This combination of polymersome and drugs self-assembles naturally when mixed. Recent studies have shown that using a combination of paclitaxel and DOX results in greater tumor regression compared to using either drug alone. Previously, no carrier system could efficiently deliver both drugs to tumors, making this approach highly promising.

11. Quantum Dots:

Single-particle quantum dots conjugated with tumor-targeting anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibodies (MAb) have been used to locate tumors through high-speed confocal microscopy (Tada H et al., 2007). After the injection of the quantum dot-MAb conjugates, six distinct stop-and-go steps were observed as the particles moved from the injection site to the tumor, where they bound to HER2. These blood-borne conjugates extravasated into the tumor, attached to HER2 on cell membranes, entered tumor cells, and traveled to the perinuclear region. The image analysis of the delivery process of individual particles in vivo provided important insights into MAb-conjugated therapeutic particles, which may help enhance their anticancer efficacy. However, the therapeutic potential of quantum dots remains uncertain.

12. Clonal Antibodies:

Over the past three decades, monoclonal antibodies (MAbs) have evolved from being valuable research tools to powerful therapeutic agents. **Muromonab CD3**, a murine MAb, was the first therapeutic MAb approved by the FDA to prevent kidney transplant rejection. Following this, the development and approval of the first chimeric MAb, **rituximab**, for the treatment of low-grade B cell lymphoma saw slower progress from its approval in 1986 until the late 1990s. However, since then, the approval process has accelerated with the introduction of chimeric, humanized, and fully human monoclonal antibodies for treating various diseases. As a result, both the pace of approval and the availability of these antibodies for clinical use have increased dramatically. In March 2017, the FDA had approved approximately 60 therapeutic monoclonal antibodies (MAbs) (Kohler G et al., 1975). By December 2019, this number had increased to 79 (Maloney DG et al., 1997), though there remains significant potential for growth in this area. The latest market trends and advancements in antibody engineering technologies are discussed, including:

- Affinity maturation
- Humanization of monoclonal antibodies
- Phage display
- Human antibody mouse technology
- Single B cell antibody technology

These innovations continue to drive progress in the development of more effective and targeted therapeutic antibodies for various diseases (Santana CP et al., 2019).

13. Dendrimers:

Early research on dendrimer-based drug delivery systems primarily focused on encapsulating drugs, but controlling drug release was challenging. Recent advancements in polymer and dendrimer chemistry have led to the development of dendronized polymers, a new class of linear polymers with dendrons attached to each repeat unit. These polymers differ from traditional linear polymers and offer benefits in drug delivery due to their prolonged circulation time. Another method involves synthesizing or attaching drugs to dendrimers, incorporating a degradable link to better regulate drug release. For example, DOX (doxorubicin) was conjugated to a biodegradable dendrimer, with its blood circulation time optimized through careful size and molecular architecture design. This DOX-dendrimer system-controlled drug loading via multiple attachment sites, improved solubility through PEGylation, and enabled drug release through pH-sensitive hydrazone linkages. In cell culture, DOX-dendrimers were over 10 times less toxic to colon carcinoma cells compared to free DOX. In tumor-bearing mice, intravenous administration of DOX-dendrimers resulted in nine times higher tumor uptake than free DOX, leading to complete tumor regression and 100% survival of the mice after 60 days (Lee CC et al., 2006).

14. Resealed Erythrocytes as Drug Carriers:

Resealed erythrocytes are biocompatible, biodegradable, and have a long circulation half-life, making them capable of carrying a variety of active therapeutic substances. Due to their numerous advantages over conventional drug delivery techniques, resealed erythrocytes are increasingly preferred as carriers. Carrier erythrocytes are produced by extracting blood from the target organism and isolating the erythrocytes from the plasma (Eicher HG et al., 1986). These cells are then processed through various techniques to trap the drug inside the erythrocytes. Once the drug is loaded, the cells are resealed and labelled as "resealed erythrocytes." This method offers great potential as a drug delivery system, enhancing patient adherence and improving the therapeutic index. Resealed erythrocytes can delay the onset of drug release while ensuring targeted delivery to specific areas, minimizing drug wastage. This approach also reduces the adverse effects of many drugs, including steroids, aspirin, and cancer treatments. The current review highlights several key aspects of resealed erythrocytes, including drug-loading methods and their diverse applications (Balasubramanian J et al., 2022). A significant amount of research is required to fully harness the potential of erythrocytes in both passive and active drug targeting, particularly for conditions like cancer. Erythrocytes have emerged as one of the most effective carriers in advanced drug delivery systems due to their remarkable capabilities. Combining genetic engineering techniques with erythrocytes can provide a more modern and enhanced approach to cellular drug carriers. Using red blood cells (RBCs) as drug carriers allows for the targeted delivery of substances, potentially minimizing the adverse effects of treatments like hormone therapies and steroid transplants. This ability to deliver drugs precisely to the desired location while reducing side effects makes erythrocytes a critical component in novel drug delivery systems, often referred to as the "golden eggs" of this field (Schrier SL., 1987).

Conclusion

A **"novel drug delivery system" (NDDS)** refers to any combination of formulation technologies, delivery mechanisms, and patient safety measures designed to deliver pharmaceutical substances into the body at the right time and location to achieve the desired therapeutic effect. The use of NDDS can be a pivotal innovation in solving challenges related to the controlled release of medications at specific sites and at predetermined rates. It is generally more efficient, cost-effective, and time-saving to modify existing excipients than to create entirely new excipient entities and evaluate them. The development of excipients that can serve multiple purposes—such as enhancing drug stability and bioavailability and controlling drug release based on therapeutic needs—is one of the key factors for advancing the design of innovative drug delivery systems. The continuous advancements in drug delivery technologies are transforming the way we approach treatment. By overcoming the limitations of traditional drug delivery methods, novel drug delivery systems offer the promise of more efficient, targeted, and personalized therapies. With ongoing research and technological innovations, the future of drug delivery systems looks bright, offering new hope for patients suffering from a variety of diseases.

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How to cite this article:
Dr Nupur Sinha et al. Ijppr.Human, 2024; Vol. 30 (10): 301-307.
Conflict of Interest Statement: All authors have nothing else to disclose.