Advances In Drug Delivery Systems, Challenges, And Future Directions: Navigating Emerging Trends For Enhanced Therapeutic Efficacy

Alnashmi Nawaf Sayer Alanazi[1], Madina Mousa Alheedr[2], Khalid Mukhlef Alanazi[3], Falah Nawaf Sayer Alanazi[4], Abdullah Qublan Sayed Alshammari[5], Saad Khalaf Alanazi[6], Mona Mustafa Jadkarim[7], Sultan Nazmi Alqutub[8], Taghreed Fawaz Alhibshi[9], Hala Nadian Alrwailiy[10], Qasem Qaed Rashed Alharbi[11], Mohammed Naif Alghamdi[12], Entesar Hadi Ali Kariri[13], Fahad Munawar Eid Al-Rashidi[14], Sahar Mohammed Alhuwaidi[15], Ahmed Hussein Azeb Alzhrani[16], Badr Zayed Al-Otaibi[17], Ali Hussain Ali Hejje[18]

1. Alnashmi Nawaf Sayer Alanazi, Pharmacy Technician, King Khlad Hospital. Ministry of health Kingdom of Saudi Arabia. Nashmi1928@gmail.com
2. Madina Mousa AlHeedr, Bachelor of pharmacy, King khalid General Hospital, Ministry of Health, Kingdom of Saudi Arabia. Madina.Alheedr@gmail.com
3. Khalid Mukhlef Alanazi, Pharmacy Technician, King Khalid General Hospital, Ministry of Health, Kingdom of Saudi Arabia. Kh_m1199@hotmail.com
4. Falah Nawaf Sayer Alanazi, Pharmacy Technician, King Khalid General Hospital,Ministry of Health,Kingdom of Saudi Arabia. falahalanzi@yahoo.com
5. Abdullah Qublan Sayed Alshammari, Pharmacy Technician, King Khalid General Hospital, Ministry Of Health, Kingdom of Saudi Arabia. Tg.e1407@gmail.com
6. Saad Khalaf Alanazi, Pharmacy Technician, King Khalid General Hospital, Ministry Of Health, Kingdom Of Saudi Arabia. Saad93353@hotmail.com
7. Mona Mustafa Jadkarim, Pharmacist, Aliman General Hospital, Ministry of Health, Kingdom of Saudi Arabia. mjadkarim@moh.gov.sa
8. Sultan Nazmi AlQutub, Pharmacist, Ministry of Health, Kingdom of Saudi Arabia. salqutub@moh.gov.sa

9. Taghreed Fawaz Alhibshi, Pharmacist, Aliman General Hospital, Ministry of Health, Kingdom of Saudi Arabia. thibshi@moh.gov.sa
10. Hala Nadian Alrwailiy, Pharmacy Technician, Al Iman General Hospital, Ministry of Health, Kingdom of Saudi Arabia. hnalrwaily@moh.gov.sa
11. Qasem Qaed Rashed Alharbi, Technician-Pharmacy, Al- Jawa Eye Hospital, Ministry of Health, Kingdom of Saudi Arabia. gassima@moh.gov.sa
12. Mohammed Naif Alghamdi, Pharmacist, Al-Iman General Hospital, Ministry of Health, Kingdom of Saudi Arabia. Ph.mohd1991@gmail.com
13. Entesar Hadi Ali Kariri, Pharmacist, Al-iman General Hospital, Ministry of Health, Kingdom of Saudi Arabia. ph.entesar24680@gmail.com
14. Fahad Munawar Eid Al-Rashidi, Pharmacist, Maternity and Children's Hospital in Hail, Ministry of Health, Kingdom of Saudi Arabia. fahad1000@live.com
15. Sahar Mohammed Alhuwaidi, Pharmacist, King Khalid Hospital, Ministry of Health, Kingdom of Saudi Arabia. Smalhuwaidi@moh.gov.sa
16. Ahmed Hussein Azeb Alzhrani, Pharmacist, Al-Iman General Hospital, Ministry of Health, Kingdom of Saudi Arabia. abuhussein1431@gmail.com
17. Badr Zayed Al-Otaibi, Pharmacy Technician, Rafaya Al Gamsh Hospital, Ministry of Health, Kingdom of Saudi Arabia. bzotaibi@moh.gov.sa
18. Ali Hussain Ali Hejje, Pharmacist, Bani Malik Hospital, Ministry of Health, Kingdom of Saudi Arabia. alihejje@gmail.com

Abstract:

Recent advancements in molecular pharmacology and a better understanding of disease mechanisms have highlighted the importance of targeting specific cells involved in disease initiation and progression. This is particularly crucial for life-threatening diseases that require therapeutic agents with potential side effects, necessitating precise tissue targeting to minimize systemic exposure. Modern drug delivery systems (DDS) utilize cutting-edge technology to enhance systemic drug delivery to targeted sites, maximizing therapeutic effectiveness while

reducing off-target accumulation in the body. These DDS play a vital role in disease management and treatment, offering significant advantages over traditional delivery systems in terms of performance, automation, precision, and efficacy. Comprised of nanomaterials or miniaturized devices with biocompatible, biodegradable, and highly viscoelastic components, these systems have an extended circulating half-life. This review provides a comprehensive overview of the history and technological progress of drug delivery systems, highlighting the latest advancements, therapeutic applications, challenges, and future directions for improved performance and utilization.

Keywords: Drug delivery system, Nanoparticles, Nanocarriers, Nanosheet, Tumour, Pharmacokinetics, Chemotherapy.

1. Introduction

Drug delivery systems are technological systems that prepare and store drug molecules in appropriate forms, such as tablets or solutions, for administration. Their purpose is to accelerate the delivery of drugs to specific target sites in the body, maximizing their therapeutic effectiveness while minimizing off-target accumulation (1,2). Drugs can be introduced into the body through various routes, including oral administration (3,4), buccal and sublingual administration (5), nasal and ophthalmic routes (6), transdermal and subcutaneous routes (7), anal and transvaginal routes (8), and intravesical administration (9). The components of a drug contribute to its physiochemical properties and are responsible for the changes it induces in the body when taken.

Over the past few decades, drug delivery systems have been successfully utilized in disease treatment and health improvement due to their ability to enhance systemic circulation and control the pharmacological effects of drugs. The advancements in pharmacology and pharmacokinetics have highlighted the importance of drug release in determining therapeutic effectiveness, leading to the development of controlled release systems (10). Controlled-release formulations were first approved in the 1950s and have since garnered significant attention because of their advantages over conventional drugs. These formulations release drugs at a predetermined rate and for a specific duration. Moreover, they are not influenced by physiological conditions and

can therefore remain active in the body for days to years. The controlled release also enables spatial control over drug release, with options for constant or variable release rates (11). Additionally, it improves drug solubility, target site accumulation, efficacy, pharmacological activity, pharmacokinetic properties, patient acceptance, and compliance, and reduces drug toxicity (2).

Recently, advanced drug delivery systems (NDDS) have been developed to achieve more convenient, controlled, and targeted drug delivery. Each drug delivery system possesses unique characteristics that determine its release rate and mechanism, primarily influenced by physical, chemical, and morphological differences that affect their affinities for different drug substances (12). Studies have identified diffusion, chemical reaction, solvent reaction, and stimuli control as major mechanisms of drug release (13,14). For example, in the case of many cancer cells, which can proliferate through porous blood vessels and the lymphatic system, drugs can easily pass through these openings to reach the target tissues. This phenomenon is known as Enhanced Permeability and Retention (EPR) (15). EPR is a well-researched passive diffusion mechanism widely used in delivering many chemotherapeutic agents. However, EPR has its limitations, such as lack of selectivity and increased toxicity. Active targeting addresses the issues of specificity and selectivity encountered in passive targeting. It involves attaching ligands and molecules to carriers that can actively bind to the surface of target tissues, thereby reducing side effects and toxicity by preventing uptake by non-target cells (16) (17). Challenges to the full development of actively targeting drugs include the selectivity of ligands to target cells, immunogenicity, and the likelihood of lysosomal degradation after macrophage endocytosis (18). These delivery systems can also reach target cells by controlling one or more physical or chemical properties through responsive stimuli targeting (19). These physical properties include pH, temperature, ultrasound, magnetic fields, and electric fields.

2. The early period of drug delivery systems

During ancient times, people relied on medicinal plants for their healthcare needs. Although these plants had beneficial properties, they had limitations in terms of consistency, uniformity, and targeted delivery of drugs. Before the development of controlled drug delivery systems, pharmaceuticals were typically produced and stored in the form of pills or capsules. Once ingested, these

formulations would dissolve upon contact with gastrointestinal fluids, pass through the intestinal wall, and enter the bloodstream through blood capillaries. However, there was no means of controlling the rate at which the drug was released. To mask the bitter taste of drugs, Rhazes and Avicenna introduced a coating technology that modified the release rate of the drug itself. This method of coating was initially employed in the 10th century, using materials such as gold, silver, and pearl to coat tablets.

In the 20th century, more advanced coating technologies were introduced, including the use of keratin, shellac, sugar, enteric coating, and pearl coating. However, keratin and shellac proved to be ineffective due to issues with storage stability and the requirement for a high pH environment for proper dissolution in the small intestine. Malm et al. (20) introduced an enteric-coating material composed of polymeric cellulose acetate phthalate, which dissolved at a weak alkaline pH similar to that of the small intestine. This made it highly suitable for enteric controlled release applications.

The initial generation of controlled drug delivery systems was highly productive and focused on the development of various oral and transdermal formulations for clinical use, as well as the establishment of mechanisms for controlled drug release. In 1951, Lipowski introduced a patented oral sustained-release formulation by coating pills with enteric polymers in a layered fashion, resulting in a slow, regular, and periodic release of the drug (21). This concept was further developed by Smith, Klein Beecham, and French (SKF) in 1952, who created Spansule technology—a predetermined-release oral formulation that provided sustained and controlled release of a drug over time. The formulation consisted of numerous micro-pellet drug-loaded beads with varying thicknesses of water-soluble wax layers on each pellet. Upon ingestion, the outer capsule would quickly disintegrate, allowing the gradual dissolution of the waxy coating as the beads traveled through the gastrointestinal tract. This would then release the drug-loaded beads. This technological advancement improved patient compliance and convenience by reducing the frequency of dosing, leading to its widespread popularity (22). Subsequently, the wax coating was replaced with more consistent synthetic polymers (23).

In 1955, Jatzkewitz reported the first nanoparticle therapeutic by developing the first polymer-drug conjugate. In the 1960s, liposomes (lipid vesicles) were discovered, marking the advent of nanocarriers (24) (25). During this period, the ALZA Corporation specialized in targeting and controlling the release of drugs at specific times and locations, rather than creating drugs themselves. In 1972, Scheffel and his colleague prepared the first protein-based microspheres, while in 1976, Peter Paul Speiser's research group utilized "micelle" and "emulsion" polymerization techniques to create drug-loaded nanoparticles and microcapsules (26). In 1977, Couvreur et al. reported the lysosomotropic effects of nanoparticles and produced the first rapidly biodegradable acrylic nanoparticles (27).

The second generation (2G) of drug delivery formulations showed promise but did not achieve the expected clinical results (10). Researchers became interested in developing drug delivery systems with constant drug release rates, self-regulation, long-term depot formulations, and nanotechnology-based formulations, particularly nanoparticle formulations. During this era, long-term depot-sustained drug release formulations for peptide/protein drugs were developed (28). Smart polymers and hydrogels were also developed to stabilize drug delivery systems affected by physiological changes such as pH, temperature, electric field, and glucose. Moreover, efforts were made to develop targeted nanotechnology drug delivery systems for tumors and gene delivery using biodegradable polymers in nanoparticle structures like polymeric micelles, chitosan, lipids, and dendrimers. The goal was to modify nanoparticles in a way that allowed direct administration into the body, leading to increased drug accumulation at the target site. While these nanotechnology-based drug delivery systems demonstrated high efficacy in controlling tumor growth in animal models, only a few drugs were approved by the FDA (5).

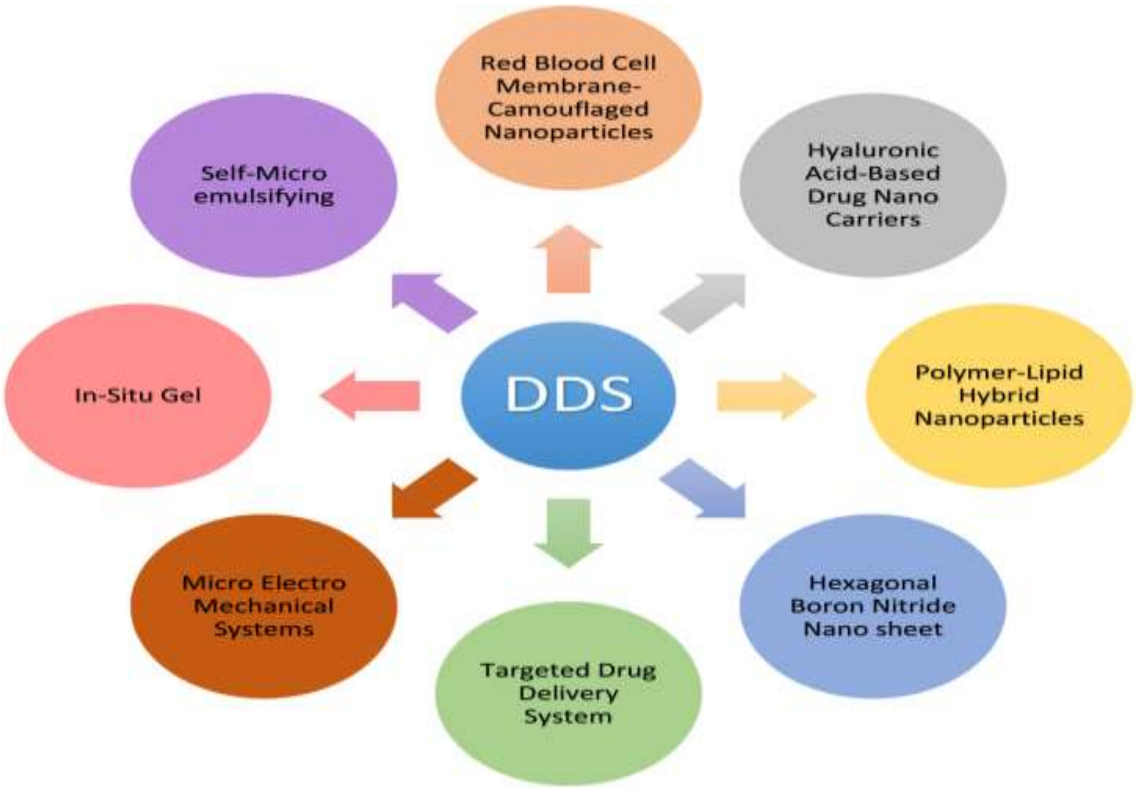
The third generation of drug delivery systems represents the modern era of controlled release technology. For these systems to be successful, they need to overcome the challenges posed by both physicochemical and biological barriers associated with earlier drug delivery systems. Physicochemical challenges include poor water solubility, high molecular weight of therapeutic proteins and peptides, and difficulties in achieving targeted and controlled drug release. Biological barrier challenges are related to issues with

systemic drug distribution (22,23). Many new drug delivery systems had to be developed during this period to address the challenges associated with earlier forms of drug delivery and improve performance and sustainability. However, designing a suitable carrier system often proves challenging due to the need to target a drug to a specific site and achieve continuous release over a specified period.

3. Recent drug delivery systems and applications

Recent advancements have led to significant progress in the development of drug delivery systems using organic, inorganic, and hybrid nanoparticles as carriers for active targeting, particularly in chemotherapy. These modern drug delivery systems (DDS) are designed with enhanced properties, including smaller particle size, improved permeability, increased solubility, efficacy, targeted site delivery, stability, reduced toxicity, and sustained release. Compared to conventional dosage forms, they offer substantial improvements in the performance of therapeutic agents (15).

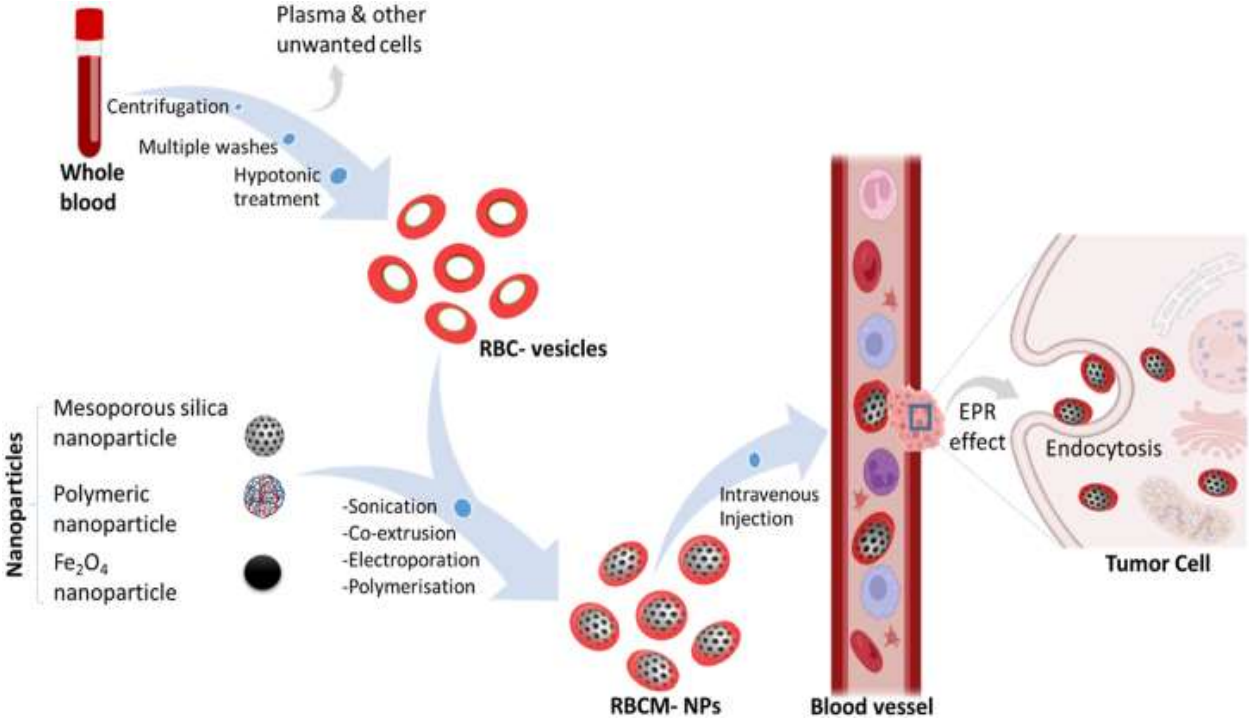
The development of an optimal drug delivery system involves incorporating the latest advancements and innovative understanding of the pharmacokinetics and pharmacodynamics of pharmaceuticals. These DDS act as transporters, maintaining therapeutic drug concentrations for extended periods and delivering the medication to the intended site of action. The successful adoption of these delivery mechanisms is crucial for both commercial and therapeutic success. It requires the early involvement of patients in the development process, addressing any potential issues, and ensuring that patients derive maximum benefits from the delivery system. The goal is to improve delivery systems that minimize toxicity while maximizing efficacy. **Figure 1** illustrates the various types of drug delivery systems available.



3.1. Red blood cell membrane-camouflaged nanoparticles for drug delivery

Over time, researchers have recognized the potential of nanotechnology to greatly enhance drug delivery methods. A novel type of drug delivery system known as red blood cell membrane-camouflaged nanoparticles has emerged. The unique properties and biological significance of red blood cells (RBCs) make them an ideal material for camouflaging nanoparticles (29). RBCs are the most abundant circulating cells in the body and possess desirable characteristics such as biocompatibility (non-immunogenicity), biodegradability, and an extended circulating half-life, making them well-suited for drug delivery purposes. Engineered RBCs have been extensively studied and proven to be excellent carriers for various bioactive substances, including enzymes, medications, proteins, and large molecules (30). By leveraging the abundance of RBCs, their membranes act as a camouflage, allowing nanoparticles to combine the advantages of native RBC membranes with those of nanomaterials. Several strategies have been developed to load therapeutic agents onto RBCs without compromising the structure and physiological function of RBCs.

Coated nanoparticles mimic RBCs and interact with the environment to achieve prolonged systemic circulation upon injection. The most common method for creating RBC camouflaged nanoparticles is sonication. Other techniques for fusing RBCs with nanoparticles include in-situ polymerization, microfluidic electroporation, and extrusion. However, each method has its advantages and disadvantages in terms of synthesis, scalability, reproducibility, and the nature of the final product (29). Before fusion, RBC membrane-derived vesicles are obtained by subjecting fresh whole blood from an organism to hypotonic treatment (such as dialysis, hemolysis, or dilution) to remove unwanted cells and plasma (Fig. 2).



The use of RBC membrane-camouflaged nanoparticles as drug delivery systems holds great promise and offers numerous advantages, including low immunogenicity and the ability to maintain prolonged systemic circulation (with a lifespan of 120 days). Additionally, due to the abundance of cell membranes, RBC vesicles are inherently biocompatible, biodegradable, and capable of achieving high drug load capacities, resulting in enhanced accumulation at the target site. Notably, erythrocyte membrane-coated nano-formulations have been extensively explored in the field of anticancer research with significant achievements (31), as

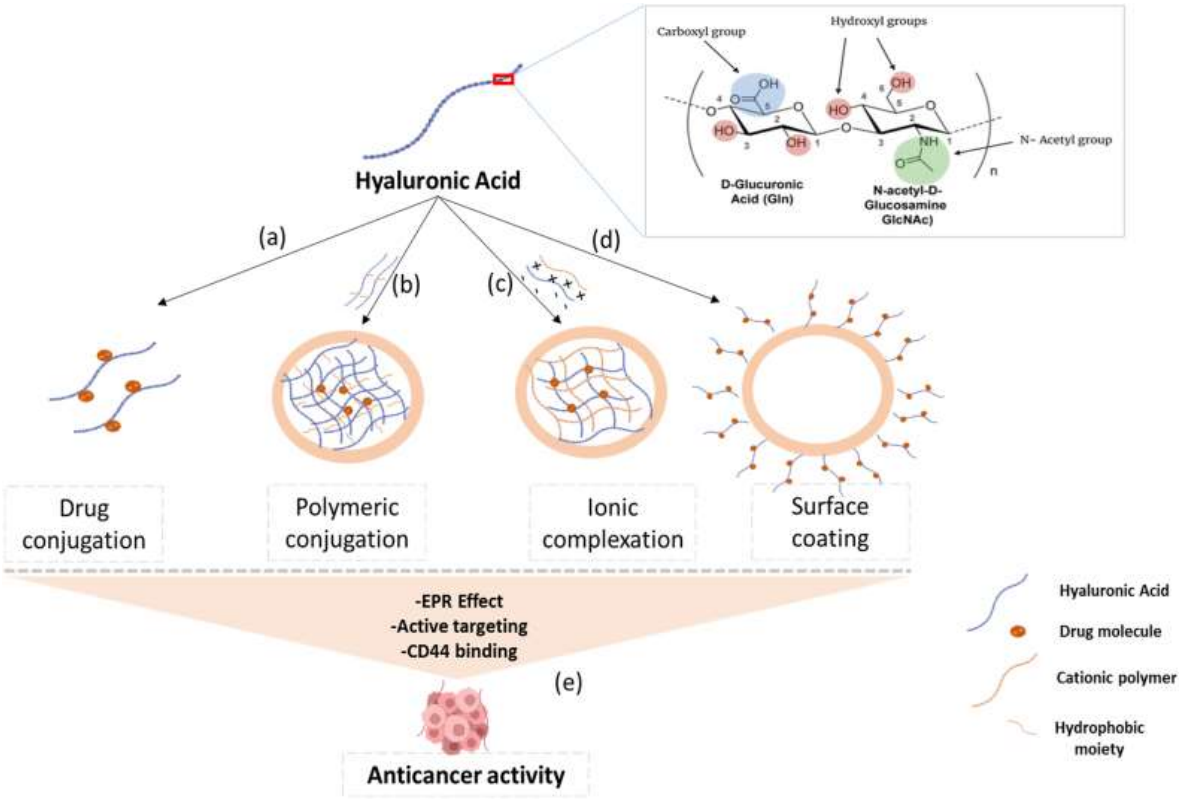
well as in the treatment of cardiovascular diseases (32) and encephalopathy.

3.2. Hyaluronic acid-based drug nanocarriers for drug delivery

Hyaluronic acid (HA) is utilized as a drug delivery technique, offering a novel approach in the field. HA is a unique polymer that can be employed to create drug delivery systems (33). It consists of a linear macromolecular mucopolysaccharide composed of interconnected glucuronic acid and N-acetylglucosamine saccharide units (34). HA exhibits biocompatibility, biodegradability, and high viscoelasticity, and it can bind to specific cell surface receptors (35). Given that HA is a natural component of eye tissue and plays a crucial role in wound healing, it is logical to utilize it as a carrier for ocular drug delivery as long as the incorporated pharmaceuticals are consistently released. HA-based systems assist in drug thickening, sustained release, transdermal absorption, and improved drug targeting. Active targeted HA-based drug nanocarriers have significantly enhanced drug distribution to cancer cells. Additionally, lipid nanoparticles with appropriate HA coatings have been developed as biocompatible drug carriers, showing great potential for targeted drug delivery to specific tissues while minimizing side effects on other tissues. Notably, utilizing HA-based nanocarriers for cancers with elevated expression of the CD44 receptor has proven beneficial, resulting in improved drug delivery, increased therapeutic efficacy, higher cytotoxicity, significant tumor reduction, and a high potential for targeted chemotherapy (36).

Another application involves combining an HA-based nanocarrier with doxorubicin (DOX) and cisplatin (CDDP) to create a CD44-targeting anti-cancer drug delivery system. In vitro and in vivo studies demonstrated the tumor inhibition activities of these dual drug-loaded HA micelles (HA-DOX-CDDP) against CD44+ breast cancer cells. The HA-DOX-CDDP micelles exhibited significantly improved drug release under acidic conditions, as well as higher cellular uptake and stronger suppression of cellular growth compared to free drugs. These micelles represent a potential drug delivery system with acid-sensitive drug release, CD44-targeted delivery, and excellent biocompatibility and biodegradability. Their characteristics enable excellent tumor accumulation and reduced side effects, indicating their potential usefulness in breast cancer chemotherapy (37,38).

Hyaluronic acid and its derivatives are incorporated into various drug delivery systems (DDS), including nanoparticle DDS, cationic polymer DDS, and gel DDS, to actively target cancer cell CD44 receptors (Fig. 3). Studies have shown that the administration of HA and drug conjugates results in their aggregation at the tumor site, where sustained drug release is maintained. The surfaces of HA-based nanocarriers are generally negatively charged, which helps prevent their systemic clearance by the reticuloendothelial system (RES). Hyaluronic acid-based drug nanocarriers selectively enter cancer cells through the enhanced permeability and retention (EPR) effect and active targeting of CD44 receptors (39).

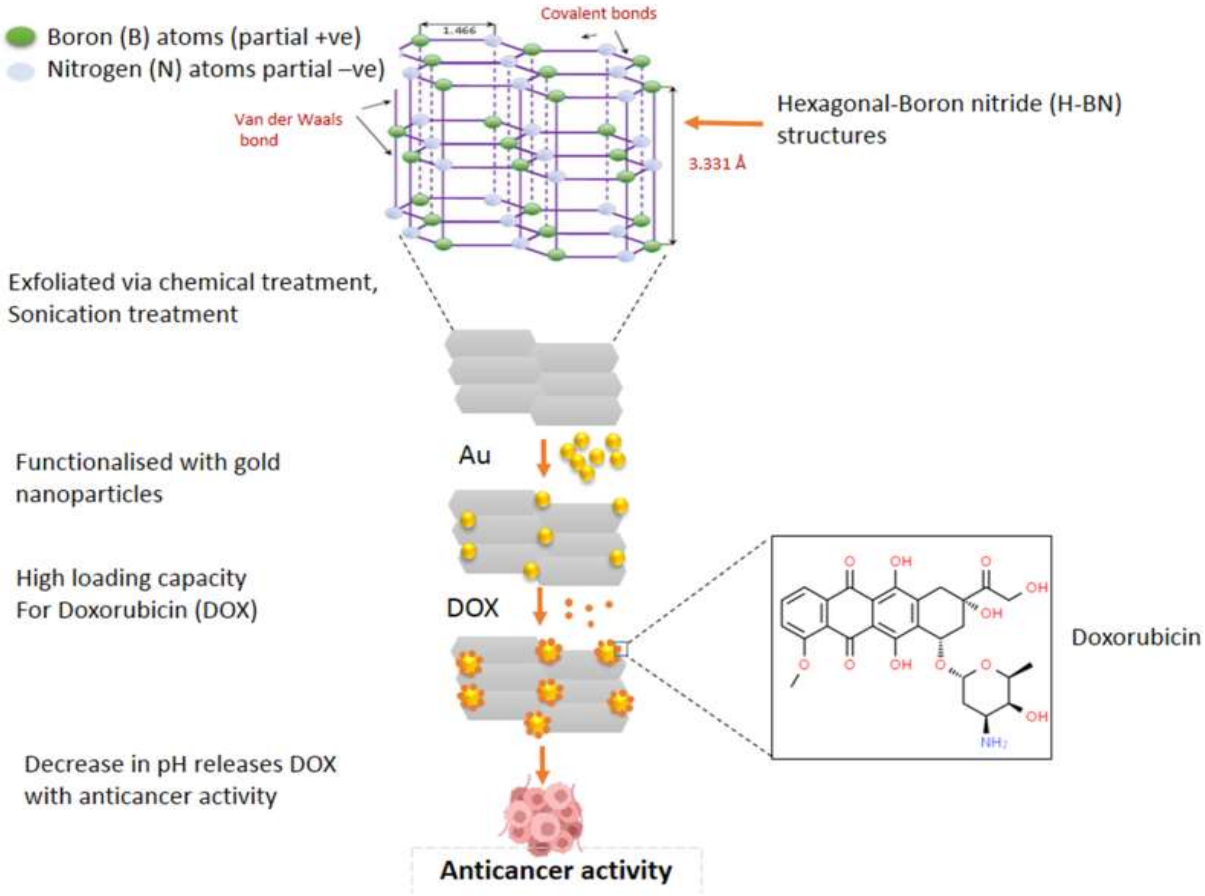


3.3. Drug delivery system utilizing hexagonal boron nitride nanosheets

As technology advances and scientific research progresses, various materials are being explored to enhance drug delivery. One such material is boron nitride (BN), a crystalline substance consisting of nitrogen (N) and boron (B) atoms in balanced stoichiometry. BN exists in different forms, including cubic BN (c-BN), hexagonal BN (h-BN), wurtzite BN (w-BN), and rhombohedral BN (r-BN).

Hexagonal boron nitride, specifically, is a two-dimensional (2D) layered structure with sp2 hybridized B-N bonds. It is often referred to as "white graphene" and shares similarities with graphite (40). The B-N atoms replace carbon atoms and form interlocking rings held together by strong covalent bonds. Van der Waals forces hold the layers of the compound together, with a bond length of 1.466 Å and an interlayer space of 3.331 Å. This compound possesses partial ionic character, resulting in polar B-N bonds. H-BN is an insulator and finds applications in various fields such as cosmetics, dentistry, cement, ceramics, and particularly in medicine as a drug carrier, similar to graphene or graphene oxide (41).

Hexagonal boron nitride has demonstrated its utility in drug research and delivery systems (Fig. 4). In a study conducted by Jedrzejczak-Silicka and colleagues, H-BN loaded with gold particles was shown to reduce the proliferation of MCF-7 cell line cultures compared to normal L929 cell lines. H-BN was exfoliated through chemical treatment using a modified Hummers' method and sonication, and subsequently functionalized with gold particles for analysis using the Neutral Red (NR) uptake assay (42). Another study involved conferring photothermal properties to H-BN nanosheets through in-situ deposition of Pd on their surface. This enabled the compound to have a high loading capacity for doxorubicin, an anticancer drug, and effectively function as a drug delivery carrier. Administration of this compound in mice for two weeks resulted in a significant inhibition of tumor growth. This was achieved by triggering the release of doxorubicin from the nanohybrids due to a decrease in pH, accompanied by an increase in glutathione concentration and near-infrared radiation (NIR) exposure (43). Furthermore, a successful study demonstrated that H-BN conjugated with DNA oligonucleotide and copper (II) phthalocyanine (CuPc) was effective as a therapeutic agent in photodynamic therapy (PDT) and for in situ monitoring and miR-21 imaging (40). Boron compounds are now recognized as effective chemotherapeutic agents.



3.4. Drug delivery system utilizing polymer-lipid hybrid nanoparticles

Nanocarriers have gained significant popularity as drug delivery systems due to their improved stability during storage, enhanced targeting capabilities for diseased cells, sustained drug release, and high encapsulation efficiency (44). Among the nanoparticles commonly used for drug delivery, liposomes, and polymeric nanoparticles are widely accepted. Liposomes, lipid-based nanoparticles, exhibit excellent biocompatibility but suffer from drug leakage and instability during storage. On the other hand, polymeric nanoparticles, which are based on polymers, address these limitations by offering high encapsulation capacity and stability. However, they exhibit lower biocompatibility (45) (46). To overcome these shortcomings and develop an effective nanomaterial, researchers have created a hybrid system that combines the unique properties of both types of nanoparticles, known as polymer-lipid hybrid nanoparticles (PLHNPs). This hybrid

system fulfills the requirements of biocompatibility, storage stability, sustained drug release, minimal drug leakage, small particle size, and high encapsulation efficiency (47). As a result of its efficacy, PLHNPs are currently utilized in various therapeutic and diagnostic applications.

PLHNPs consist of three distinct components: a polymeric core that effectively encapsulates both hydrophilic and hydrophobic drugs, a lipid shell that provides biocompatibility and high stability, and a lipid-polyethylene glycol (PEG) outer layer that enhances steric stability, prevents immune recognition, and prolongs circulation time. PLHNPs find wide application in the delivery of various chemotherapeutic agents, gene transfer (siRNA, DNA), photothermal and photodynamic therapy, ultrasound, vaccine delivery, immune activation, imaging, and alternative magnetic field (AMF) applications. They have become essential in the rapidly advancing medical field (48).

3.5. Self-microemulsifying drug-delivery system

Lately, there has been significant interest in lipid-based drug preparations, particularly in self-microemulsifying drug-delivery systems (SMEDDS)(49). Developing oral dosage forms that provide adequate bioavailability is challenging, as drugs need to be in solution form to be absorbed through the gastrointestinal tract (GIT)(50,51). Many pharmacologically effective compounds have poor aqueous solubility, which poses a problem(52). In fact, around 30% of widely marketed medicinal products and nearly 50% of innovative drug compounds available for manufacturing are hydrophobic, meaning they have low water solubility(53). To enhance the bioavailability of these less water-soluble drugs, the use of a lipid-based carrier system has gained popularity(54). The primary objective of this formulation is to maintain the hydrophobic components in solution throughout the digestive system(53).

Lipid-based carriers can take various forms, including suspensions, dry emulsions, microemulsions, and self-emulsifying drug-delivery systems (SEDDS)(55). SEDDS have been recognized for their ability to incorporate hydrophobic drugs. Over time, SEDDS has evolved into self-microemulsifying drug-delivery systems (SMEDDS) and self-nanoemulsifying drug-delivery systems (SNEDDS). Emulsions, on the other hand, are created by dispersing a liquid phase containing visible particles within a different liquid phase that

consists of a surfactant (56). Emulsions are thermodynamically unstable solutions, typically semi-transparent or occasionally hazy, and exhibit properties similar to viscous liquids(57). Emulsions can be classified into three types: water-in-oil, oil-in-water, and multiple emulsions. It's worth noting that conventional micro- or nanoemulsions differ from SMEDDS in that they self-emulsify after oral ingestion.

Microemulsions (Figure 6) in lipid-based carriers rely on two types of emulsifying agents: surfactants (S) and co-surfactants (CoSs). Surfactants are predominantly soluble in water, while co-surfactants are mainly soluble in the oil phase. Co-surfactants play a crucial role in reducing the interfacial tension between the two liquid phases to the optimal level required for microemulsion formation(58,59). On the other hand, producing nanoemulsions with droplet sizes smaller than 100 nm requires either mechanical or chemical energy(60). Nanoemulsions are considered kinetically stable due to their extremely low rate of destabilization, and they exhibit long-term stability lasting several months. As a result, nanoemulsion droplets demonstrate stability under various conditions such as different dilutions and temperatures, whereas microemulsions are more susceptible to factors like dilutions and temperature variations(57,61). **Table 1** provides a clear overview of the key differences among SMEDDS, SNEDDS, and SEDDS.

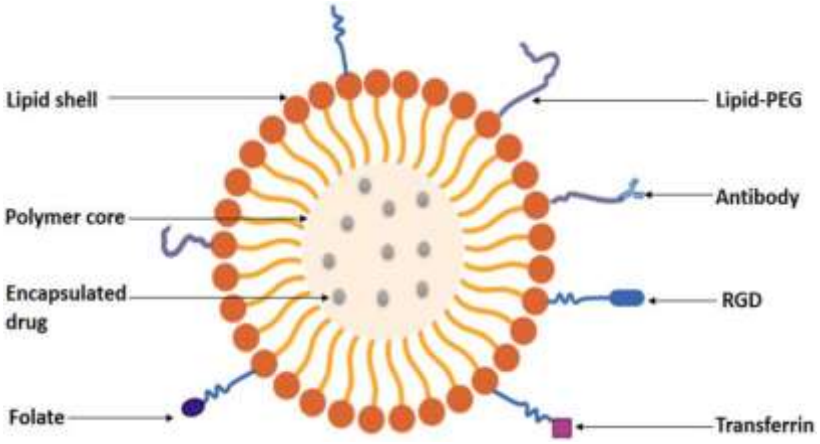


Figure 5 depicts the process of creating a Polymeric-Lipid Hybrid Nanoparticle. This hybrid nanoparticle consists of three main components: Polymeric core: The central part of the nanoparticle acts as a polymeric core. It efficiently encapsulates both hydrophilic and hydrophobic drugs. The polymeric core provides effective drug delivery and protection, Lipid shell: Surrounding the polymeric core is a lipid shell. This lipid layer enhances the biocompatibility of the nanoparticle and contributes to its overall stability. The lipid shell provides a protective barrier around the core and Lipid-polyethylene glycol (PEG) outer layer: The outermost part of the nanoparticle is composed of a lipid-polyethylene glycol (PEG) layer. This layer is covered by a lipid coating. It serves multiple purposes, including increasing steric stability, preventing immune recognition, and extending circulation time within the body.

Figure 6 demonstrates the mechanism of self-emulsification in an aqueous environment. Self-emulsifying drug delivery systems (SEDDS) consist of a combination of drugs, surfactants, oil, stabilizers, and cosolvents. Similar to conventional emulsification, SEDDS, which is an ionotropic mixture, spontaneously form nano or microemulsions in the gastrointestinal tract with minimal energy input. These emulsions are typically of the oil-in-water (o/w) type.

Table1 Four basic types of lipid-based drug-delivery systems (LBDDS) with their merits and demerits

Characteristics	SMEDDS	SNEDDS	SEDDS
Size of the globule	<250 nm	<100 nm	>300 nm
The system appearance	High Optical clarity	High Optical clarity	Cloudy
The surfactant HLB value	>12	>12	<12
LFCS Classification	Type IIIB	Type IIIB	Type II
Oil phase	>20%	>20%	40–80%
Surfactants Concentration	40–80%	40–80%	30–40%

HLB=Hydrophilic/lipophilic balance; LFCS = lipid formulation classification system; SEDDS = self-emulsifying drug-delivery systems; SMEDDS = self-microemulsifying drug-delivery systems; SNEDDS = self-nanoemulsifying drug-delivery system(53).

3.6. In-situ gel drug delivery system

The primary objective of drug delivery systems is to modify the pharmacokinetic characteristics and tissue distribution of drugs in a significant way(62). Over the past six decades, considerable efforts have been dedicated to developing controlled and reliable drug delivery systems(63). Among these systems, in-situ gel medication administration has emerged as an innovative approach. The unique property of in-situ gels, transitioning from a solution to a gel state, allows for prolonged and controlled drug release, improved patient compliance, and enhanced comfort(64). Typically, formulations in solution form undergo a transformation into a gel state under specific physiological conditions before entering the body(65). Various stimuli, such as changes in pH, temperature modulation, and solvent exchange, can induce the conversion of a solution into a gel form(66). In research, different

administration routes have been explored, including oral, nasal, injectable, vaginal, rectal, ocular, intraperitoneal, and parenteral routes, utilizing a range of polymeric methods for drug delivery. These polymers undergo a sol-gel transition when exposed to physiological stimuli. In-situ gel drug delivery systems are formulated using natural and synthetic polymers(64). The formation of in-situ gel biomaterials can occur through four processes: 1. temperature and pH variations, 2. changes in the physical properties of the biomaterials such as solvent exchange and swelling, 3. biochemical modifications involving enzymatic and chemical reactions, and 4. photo-polymerization(67).

Oral in-situ gel delivery systems focus on using pH-sensitive hydrogels to target specific regions of the gastrointestinal tract for site-specific drug delivery. For instance, silicone microsphere hydrogels containing different amounts of Polyacrylic acid (PAA) derivatives and cross-linked Polyethylene glycol (PEG) have been developed to release prednisolone in the stomach media or exhibit gastroprotective properties. Additionally, dextran hydrogels cross-linked with polysaccharides like guar gum, inulin, and amide pectin have been explored as a potential approach for colon-specific drug delivery to reduce edema at high pH. Researchers have also developed gellan gum and sodium alginate formulations that utilize calcium ions as complexing agents, leading to gelation upon their release in the acidic medium of the stomach. Natural polymers like xyloglucan, pectin, and gellan gum are employed in oral in-situ gel delivery methods. Specifically, a pectin-based formulation has been designed to achieve sustained release of Metformin loaded pectin (PCM) without the need for organic solvents due to the water-soluble nature of pectin(68,69).

Ophthalmic in-situ gelling systems employ natural polymers such as gellan gum, alginic acid, and xyloglucan. These systems are used for local administration in the treatment of intraocular glaucoma, combining various anti-inflammatory, antibacterial, and autonomic medications. The rapid turnover and dynamics of tear fluid pose challenges to the bioavailability of ocular in-situ gels. Traditional delivery methods have limited availability and therapeutic response, resulting in the easy removal of the medication from the eye. Viscosity enhancers like Carboxymethyl Cellulose, Polyvinyl alcohol, Carbomers, and Hydroxypropylmethyl cellulose are utilized in ocular preparations to improve the viscosity of drug

formulations, leading to enhanced bioavailability and prolonged precorneal residence duration. Chelating agents and penetration enhancers are employed to promote the penetration of corneal substances, such as surfactants and preservatives(70,71).

In nasal in-situ gelling systems, polymers like gellan gum and xanthan gum are used. The effectiveness of in-situ gels containing Momethasone furoate in managing allergic rhinitis has been studied. In vivo experiments using sensitized rats as a model of allergic rhinitis have demonstrated the ability of in-situ gels to reduce nasal symptoms compared to commercialized preparations of Nosonexex(72).

Rectal in-situ gelling systems offer a means to administer various pharmaceuticals in liquid, semi-solid, or suppository form. Traditional suppositories can cause discomfort during insertion and may migrate upward into the gut, leading to the drug's first-pass effect. Xyloglucan-based devices loaded with Indomethacin have shown significant drug absorption and prolonged residence time compared to commercial suppository administration(73).

Vaginal in-situ gelling systems are developed for the continuous release of active substances such as estrogens, peptides, progestins, and proteins. A thermoplastic graft copolymer-based delivery system undergoing in-situ gelation has been formulated. The combination of poloxamers and polycarbophils in mucoadhesive thermosensitive gels has been shown to enhance and sustain the antifungal efficacy of clotrimazole compared to conventional polyethylene glycol-based formulations(74).

Injectable in-situ gelling systems, such as thermo-reversible gels made of poloxamers, are used for prolonged drug release. They have been tested with insulin or insulin-PLGA nanoparticles and have also been employed for subcutaneous and intramuscular delivery of human growth hormone. New formulations combining poly(D,L-lactide)/1-methyl-2-pyrrolidone solutions have been developed for controlled release injectables. Injectable drug delivery methods are used to cross-link pluronic acid-modified hydrazide with aldehyde-modified cellulose derivatives, aiming to reduce postoperative complications such as peritoneal adhesion and pelvic discomfort(75).

3.7. Micro electro mechanical systems (MEMS) for drug delivery

EMS technology finds extensive use in various fields, including actuators, drug delivery, motion sensing, accelerometers, and inkjet printing(76). These applications involve the creation of small electromechanical and mechanical devices or implants using microfabrication techniques(77). These techniques provide significant advantages by enabling precise control over the devices' topography, microarchitecture, and size(78).

MEMS-based devices utilize a variety of materials and processes for their design. These devices incorporate a combination of micromachining techniques such as deposition, etching, lithography, ink jetting, ion implantation, oxidation, and micromolding(79,80). In the context of drug delivery systems, MEMS technology enables the fabrication of miniaturized systems using materials like silicon, glass, metals, nitrides, and polymers. These systems consist of components such as micropumps, sensors, microvalves, reservoirs, actuators, and high-performance processors(81,82). These components work together synergistically to provide the multi-functionality and precision that MEMS devices offer compared to conventional drug delivery systems.

Each component serves a strategic purpose in the overall functionality of the MEMS-based drug delivery device. Actuators, for example, play a vital role in the drug release process by pressurizing the drug reservoir to facilitate drug release(83). Reservoirs provide ports to house the drugs and can be designed as single or multiple reservoir architectures. A single reservoir architecture features a relatively large port capable of containing a single drug, allowing for a larger amount of drug and refillable options for long-term usage. On the other hand, multi-reservoirs have different ports within the same substrate, enabling the storage of multiple drugs. However, they are less suitable for long-term usage as they require repetitive replacement surgeries due to the absence of refilling methods. Microvalves are employed to control fluid flow rate, sealing, and the on/off switching of the delivery device(84). Silicon is a commonly used substrate or structural material in MEMS fabrication due to its favorable mechanical and electrical properties. Sensors utilize various mechanisms such as electrical radiation, mechanical, thermal, magnetic, or biochemical methods to monitor the flow

measurements of fluids or gases being delivered(85). Therefore, the selection and design of each feature during the device's development process are crucial for achieving the desired functionality of the MEMS-based drug delivery device.

MEMS-based devices have crucial roles in achieving targeted and precise drug delivery by enabling controlled and pulsatile release of pharmaceuticals(86). These devices can be designed as either electric-powered or non-electric powered systems. Electric-powered devices utilize electric potential to selectively release drugs from reservoirs, while non-powered devices rely on diffusion and osmotic environmental stimuli for drug release(81). Among MEMS technologies, microchips are the most popular for drug delivery, followed by microfluidic devices, particularly micropumps. Microchips are implantable reservoir-based devices capable of delivering drugs in solid, gel, or liquid forms through transdermal or intradermal delivery. Micropumps, categorized as mechanical or non-mechanical based on the presence of moving parts, are specifically used for delivering drug suspensions or solutions(82).

MEMS-based drug delivery devices offer numerous advantages over conventional methods, including enhanced performance, automation, precision, efficacy, and reduced invasiveness due to their miniaturized size and integration of multifunctional components(81). They maintain drug stability during encapsulation, enable adjustable and continuous drug delivery, facilitate automated release of multiple drugs from reservoirs, enhance bioavailability, and allow localized release of medication(78). These devices also support long-term sustainability for complex dosing requirements, personalized dosing profiles, and exhibit sustained zero-order kinetics. However, there are technical challenges associated with incorporating wireless electronics for remote control and tracking, which can increase device security risks, as well as challenges related to medical packaging and regulatory complexities(81). Additionally, implantation and removal of these devices require surgeries, highly stable products are necessary for long-term usage, and the fabrication technologies involved can be relatively expensive(87).

3.8. Combined drug delivery approach

Drug resistance has been a persistent problem in medical treatment, prompting the adoption of combination therapy for

improved efficacy and clinical outcomes. Combining multiple drugs in a single delivery approach has gained popularity, particularly in cancer research to overcome multidrug resistance. Studies have shown that combination drug delivery approaches can reduce therapeutic dosages and adverse reactions while maintaining efficacy and reducing drug resistance(88).

One study by Zamora-Mera et al. focused on magnetic hyperthermia therapy and utilized crosslinked chitosan nanoparticles (CSNPs) combined with tripolyphosphate salts (TPP). They encapsulated the CSNPs with different concentrations of ferrofluid and a constant concentration of 5-Fluorouracil (5-FU). The study successfully demonstrated dose-dependent cytotoxicity of the CSNPs in both normal fibroblast cells (FHB) and cancer cells (human glioblastoma A-172 cells). The combination of magnetic hyperthermia treatment with CSNPs loaded with ferrofluid and 5-FU resulted in a significant decrease in cell viability in cancer cells compared to normal cells, indicating the effectiveness of the combination approach in overcoming drug resistance(89).

Silva et al. conducted a study investigating the combined method of affinity purification with Endotrap-HD resin and treatment with Triton X-144 to remove endotoxins from protein nanocages for drug delivery applications. The combination treatment showed promising results, highlighting its potential in chemotherapy(90).

In a review article by Pang et al., the focus was on combining cells with nanoparticles for drug delivery. The review emphasized that nanoparticles loaded into cells were more effective than conventional nanoparticle drug delivery systems. Cell-based therapy demonstrated improved drug efficacy, extended half-lives, sustained drug release, and limited immunogenicity and cytotoxicity. The combination of nanoparticles with exploit cells did not compromise their migration or chemotaxic ability, suggesting the potential of combination drug delivery approaches in drug research and medical therapy(91).

3.9. Targeted drug delivery system

The targeted drug delivery approach is a recent and efficient technique that aims to increase drug concentration at the intended site while minimizing side effects. It involves delivering drugs in a specific sequence to achieve optimal efficacy without compromising strength. Various drug carriers such as soluble

polymers, biodegradable microsphere polymers, neutrophils, liposomes, micelles, and artificial cells are employed in this approach. This technique is particularly valuable in cancer treatment and is gaining widespread acceptance.

Murugun conducted a study demonstrating the effectiveness of this drug delivery system. They used polyacrylic acid chitosan surface-modified mesoporous silica nanoparticles (MSN) to deliver Topotecan (TPT) and quercetin (QT) to target negative breast cancer cells (TNBC) and multidrug-resistant breast cancer cells (MCF-7). The nanoparticles' surface was modified with RGD-peptides, which effectively targeted αvβ3 integrin. The RGD peptide facilitated the release of encapsulated drugs and their uptake by cancer cells, resulting in cell death, molecular and structural changes in the cellular nucleus, endoplasmic reticulum, and mitochondria. The study also observed a synergistic antiproliferative effect(92).

Another study by Wu et al. demonstrated enhanced release of methotrexate (MTX) from Fe3O4MgAl-LDH (layered double hydroxide) nanoparticles of approximately 230 nm. They achieved 84.94% release of MTX in a tumor environment with a pH of 3.5 within 48 hours. The study showed higher antitumor activities across the investigated cell lines(93). Lin et al. targeted HeLa cells using a folate-functionalized soybean phosphatidylcholine micellar nano formulation to co-deliver mitomycin C (MMC) and 10-hydroxycamptothecin (HCPT). They observed enhanced cellular uptake both in vitro and in vivo, as well as a significant decrease in tumor burden compared to free drugs(94). These studies and others highlight the importance of targeted drug delivery systems.

4. Challenges associated with current drug delivery systems

In recent years, significant progress has been made in developing drug delivery systems that effectively target specific sites in the body for treatment. However, these systems face several limitations and challenges. One major challenge is the lack of comprehensive and standardized literature on nanomedicine approaches, which hinders research advancement and the translation of experimental findings into clinical applications. Additionally, the safety aspects of nanoparticles, including their interactions with non-specific proteins and their behavior in non-target organs, remain poorly understood(95,96).

Some drug delivery systems utilize large particles as carriers, which can pose challenges such as poor absorption and solubility, in vivo instability, low bioavailability, difficulties in target-specific delivery, and potential adverse side effects. Using smaller particles for delivery addresses these issues(97).

Achieving target-specific delivery is a common challenge across all delivery systems. While it can reduce toxicity and improve treatment efficacy, ensuring sufficient delivery to the intended site remains uncertain. Systemic administration of siRNA, for example, often results in limited absorption by target cells or organs due to enzymatic degradation and hindered cellular absorption caused by the negative charge of siRNA. Lipid nanoparticles like micelles and liposomes, which are being studied for targeted drug delivery, can be hindered by reactions with the body, such as phagocytic absorption and hepatic filtration, leading to delivery failure and potential toxicity. Furthermore, challenges such as patient unconsciousness, low solubility and permeability at the target site, interaction with food, and degradation by gastrointestinal flora further complicate targeted delivery(98).

Toxicity is a significant challenge associated with the use of particles in drug delivery systems. Nanomaterials such as silver, gold, silica, and titanium have demonstrated harmful effects on human health and the environment. Carbon nanotubes, while useful in gene therapy, bio-imaging, and drug delivery, raise concerns due to potential harm to embryos, genes, liver, heart, neurons, and the immune system. Despite their favorable properties, extensive toxicity testing is crucial before their widespread application in treatment, especially for cancer treatment where their effects have become a hindrance.

Biocompatibility and acceptability are major challenges for drug delivery systems. The body's response to biological materials differs from synthetic materials, and achieving compatibility and acceptance poses difficulties. Natural barriers within the human system, such as the blood-brain barrier (BBB), limit the delivery of therapeutic drugs to brain tissues. The BBB prevents carrier particles from entering the brain, making it challenging to achieve effective drug concentrations for cerebral diseases. Monoclonal antibodies (mAb), abundant carriers in the body, form immunoliposomes by binding to liposome surfaces. However, their

functions are limited due to potential immune responses and low absorption, distribution, metabolism, and elimination rates, posing challenges for liposomes as site-specific drug carriers(99).

The kidney and liver, which naturally detoxify the body, can treat nanoparticles as potential waste products, leading to obstruction in drug delivery and nanoparticle accumulation in these organs. Nanomaterials primarily accumulate in various liver cells, including Kupffer cells, sinusoidal endothelial cells, hepatic stellate cells, and hepatocytes. In the kidney, the size, charge, and shape of nanomaterials determine their fate within the renal system(100).

5. Future directions and conclusion

Drug delivery and nanomedicine have gained significant attention in research and clinical trials due to their potential in improving treatment outcomes(101). However, there are challenges that hinder their clinical application. To address these challenges, collaboration among various fields such as academia, medicine, and pharmaceuticals is crucial. Cell therapies have been proposed as a solution to enhance bio-acceptability and reduce drug accumulation, offering sustained release of complex biologics and overcoming biological barriers. Inorganic mesoporous nanoparticles, microfluids, and molecular imprinting polymers are suggested as potential strategies to overcome drug delivery challenges(102). Priming agents that modify the biological environment at the administration site have been proposed to improve drug delivery efficacy without harming the patient. Additionally, the integration of cell-based drug systems with nano biomaterials shows promise in achieving optimal drug delivery patterns. However, further research and clinical trials are required to enhance the efficiency of modern drug delivery systems and address the existing challenges.

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