Section A-Research paper
ISSN 2063-5346

Advances in Drug Delivery Systems: Enhancing Efficiency and Targeted Therapeutics

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DOI: 10.48047/ecb/2023.12.si4.1477

Abstract

The current paper provides an overview of the recent advances in drug delivery systems with a focus on enhancing efficiency and achieving targeted therapeutics. The field of drug delivery has witnessed significant advancements in recent years, aiming to improve drug efficacy, reduce side effects, and increase patient compliance. The paper emphasizes the need of efficient drug delivery systems in overcoming various challenges associated with conventional drug administration and innovative approaches to optimize drug delivery. Now a day the various strategies are employed to achieve site-specific drug delivery, including passive and active targeting approaches with the possibility of externally controlled release mechanism. Passive targeting exploits the unique physiological characteristics of the target site, such as enhanced permeability and retention effect, while active targeting employs ligands, antibodies or physical system to selectively deliver drugs to specific cells or tissues. In recent years the utilization of nanotechnology in drug delivery systems is becoming choice of research as they provide enhanced drug stability, controlled release, and enhanced targeting capabilities. The paper discusses the design principles, fabrication methods, and challenges associated with nanotechnology-based drug delivery systems. The paper provides a comprehensive overview of the recent advances in drug delivery systems, emphasizing their role in enhancing efficiency and proposes a model for achieving targeted therapeutics.

Keyword: Nanoparticle, Magnetic Nanomaterials, Drug Delivery System, Chemotherapeutic Drugs, Drug Delivery Vectors

1 Introduction

Nanomedicine is a field of medicine that involves the application of nanotechnology in the prevention, diagnosis, monitoring and treatment of diseases. It combines the principles of physics, chemistry, biology, engineering and medicine to create innovative solutions for healthcare. Nanotechnology deals with materials and devices at the nanometer scale, which is extremely small, typically in the range of 1 to 100 nanometers where they maintain their crystalline state but have size dependent, dramatically different properties than the bulk counterpart. At this scale, materials exhibit unique properties and behaviors, allowing scientists to manipulate, tune and engineer them for specific applications.

In nanomedicine, nanoparticles and nanoscale devices are used to interact with biological systems at the molecular and cellular levels. These nanomaterials can be designed to have specific properties, such as controlled release of drugs, targeted delivery to specific cells or tissues, and enhanced imaging capabilities.

Initial tests of various drug delivery systems, like treatment of cancer/tumor or detection have been successful using nanotechnology. Nanoparticles being very small are easy to inject and guide, with the help of external stimulator or ligands attached to it, towards specific portion in the body. Generally, drugs are attached to nanocarriers and targeted towards desired part of the body. On the way, the nanocarrier is guided to the affected area by using either external stimulator like magnetic field or ligands attached to it. At the desired location drug is released on the affected area by using some internal stimulus like physiological conditions of the affected area or external stimulus like magnetic field, IR wave etc..

A conventional drug delivery system has limitations like lack of selectivity and poor biodistribution. These limitations and drawbacks can be overcome by nano drug delivery system or controlled drug delivery system (DDS) to transport the drug to the affected area thus minimizing side effect on vital tissues. Also, DDS protects the drug from rapid degradation due to overstaying in the system, higher drug concentration at the affected area which lowers the dose quantity needed. It also helps in fast removal of the drug and the drug residue left. Recent developments in nanotechnology have shown that nanoparticles have a great potential as drug carriers [1, 2]. The oldest and still most vivid subfield is applications of magnetic nanoparticles in medical applications such as cell separation, drug targeting, electromagnetic hyperthermia, magnetic resonance contrast enhancement [3].

The targeted drug delivery systems can be passive, based on specific properties of pathological tissues or specific character of the targeted organ, or active, often

magnetically directed as magnetic targeting or magnetic drug delivery, based on various carrier systems. For example, inflated tissues or tumor differ from healthy tissue concerning pH, temperature or permeability of vascular endothelium. This enables the use of pH or thermosensitive nanoparticles to concentrate the drug in the respective tissue [4].

For systematic delivery of drugs, it is required that the nanoparticles circulate for longer time in blood without occluding arteries, veins, or capillaries, and the physical components must be non-toxic, biocompatible, biodegradable, and acceptable for human medication in all other aspects. In designing drug delivery systems for cancer therapy, it is preferred to opt for composite nanoparticles that are characterized by a functionalized magnetic core and a biodegradable polymer shell because the uncovered anticancer drugs can lead to possible side effects during the delivery of the drugs [5, 6].

2 Nanocarriers used in Drug Delivery System

2.1 Nanocarriers

Nanocarriers refer to small-sized vehicles or systems designed to transport and deliver therapeutic agents, such as drugs or genes, at the nanoscale level. These carriers are typically in the range of 1 to 100 nanometers and can be fabricated from various materials, including lipids, polymers, metals, or inorganic substances. Nanocarriers offer several advantages for drug delivery, including improved drug stability, controlled release, enhanced solubility, and targeted delivery to specific tissues or cells. Nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules. The way of attaching the medicine to the nanocarrier and the mechanism of targeting is of importance in DDS. A nanocarrier is covalently attached, adsorbed on its surface or encapsulated in it. Attaching the drug by mean of covalent bond is better than other as it allows only limited number of drug molecules to get attached to nanocarriers. This makes possible to control the amount of which can be attached and delivered, therefore. It is generally accepted that nanoparticles with a hydrodynamic diameter of 10–100 nm have optimum properties for DDS. Smaller nanoparticles are subjects to tissue extravasations and renal clearance whereas larger are quickly opsonized and removed from the bloodstream via the macrophages of the reticuloendothelial system [1,7].

There are several types of nanocarriers used in drug delivery. Here are some commonly utilized nanocarriers:

2.1 Liposomes

Liposomes are the first to be investigated as nano drug carriers. They are nano/micro-particular or colloidal carriers, usually with 80–300 nm size range. Liposomes are spherical vesicles composed of lipid bilayers. They are self-assembled structures formed by the organization of amphiphilic molecules, which have both hydrophobic and hydrophilic regions. The hydrophobic tails of the lipid molecules face inward, creating a

lipid bilayer, while the hydrophilic heads face outward, interacting with the surrounding aqueous environment. Liposomes have a hollow core that can encapsulate hydrophilic drugs or biomolecules, while hydrophobic drugs can be incorporated within the lipid bilayers. This unique structure allows liposomes to serve as effective carriers for a wide range of therapeutic agents, including small molecules, proteins, peptides, and nucleic acids. Liposomes have been reported to increase the solubility of drugs and improve their pharmacokinetic properties, such as the therapeutic index of chemotherapeutic agents, rapid metabolism, and reduction of harmful side effects and increase of *in vitro* and *in vivo* anticancer activity. The release of a drug from liposomes depends on the liposome composition, pH, osmotic gradient, and the surrounding environment. Additionally, a prolonged residence time increases the duration of action of such particles, but decreases their number. Interactions of liposomes with cells can be realized by: adsorption, fusion, endocytosis, and lipid transfer [1]. There are a lot of drug examples in liposomal formulations, such as anticancer drugs, neurotransmitters (serotonin), antibiotics, anti-inflammatory, and antirheumatic drugs.

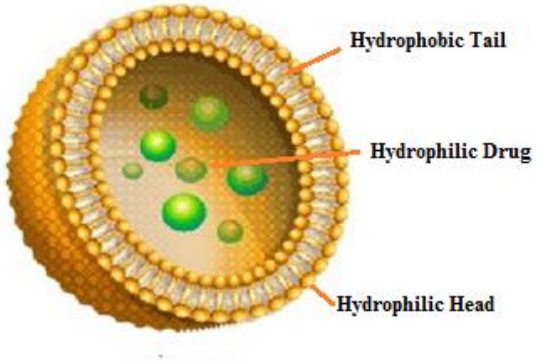

Fig. 1: Liposome

The multifunctional liposomes, containing the specific proteins, antigens, or other biological substances, can be used to design drugs which act selectively on a particular tissue [8].

2.2 Solid Lipids

Solid lipids, also known as lipid solids, are lipids that are in a solid state at room temperature [1]. Unlike liquid oils, which are in a liquid state at room temperature, solid lipids have a higher melting point due to their higher degree of saturation and/or longer fatty acid chains. Solid lipids are widely used in various applications, including food, cosmetics, and pharmaceuticals. In the context of drug delivery, solid lipids are particularly interesting because they can be utilized as carriers or matrix materials to encapsulate and deliver drugs or active ingredients. Solid lipid nanoparticles, nanostructured lipid carriers and lipid drug conjugates are the nano carrier systems based on solid lipid matrix. The main characteristics of include a good physical stability, protection of incorporated drugs from degradation, controlled drug release, and good tolerability [9].

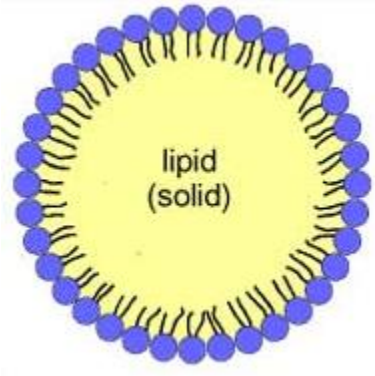

Fig. 2: Solid Lipid Nanoparticle

2.3 Polymeric Nanoparticles

Polymeric nanoparticles are nanoscale particles composed of biocompatible and biodegradable polymers with a diameter ranging from 10 to 100 nm. These nanoparticles are engineered structures that can encapsulate drugs or therapeutic agents for targeted drug delivery, controlled release, and improved bioavailability. Polymeric nanoparticles are typically made from polymers such as poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), poly (lactic acid) (PLA), chitosan, or polycaprolactone (PCL). These polymers are biocompatible, biodegradable, and can be tailored to control the release of encapsulated drugs. They can encapsulate a wide range of drugs, including hydrophobic and hydrophilic compounds. The drugs can be encapsulated within the polymer matrix, dispersed throughout the particle, or chemically conjugated to the polymer backbone. This flexibility allows for efficient loading of various therapeutic agents. Also the polymer properties, such as molecular weight, composition, and degradation rate, can be adjusted to modulate the release profile of the encapsulated drug. This control allows for sustained release over extended periods or targeted release at specific sites. Moreover, drugs may be released by desorption, diffusion, or nanoparticle erosion in target tissue.

The application of biodegradable nanosystems for the development of nanomedicines is one of the most successful ideas. Nanocarriers composed of biodegradable polymers undergo hydrolysis in the body, producing biodegradable metabolite monomers, such as lactic acid and glycolic acid. Drug-biodegradable polymeric nanocarrier conjugates used for drug delivery are stable in blood, non-toxic [10].

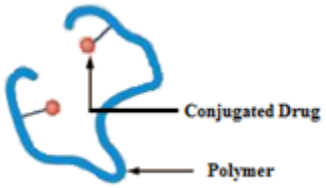

Fig. 3: Polymeric Nanoparticle

2.4 Dendrimer Nanocarriers

Dendrimer nanocarriers are a type of nanoscale delivery system based on dendrimers where the dendrimers are highly branched, tree-like structures with a well-defined and symmetric architecture. Some of the examples of nanometric molecules possessing dendritic structure include: glycogen, amylopectin, and proteoglycans. In the structure of dendrimer, in contrast to the linear polymer, the following elements can be distinguished: a core, dendrons, and surface active groups. The core is a single atom or molecule (only if it has at least two identical functional groups) that dendrons are attached to. The dendrons (dendrimer arms) are molecules of monomer linked with the core, forming layers and building successive generations (their growth is spatially limited). Dendrimers are designed to have a high degree of control over their size, shape, and surface functionalities. Dendrimers can be synthesized with precise control over their size, molecular weight, and surface functionalities. This allows for a tailored design and optimization of properties, such as drug loading capacity, solubility, stability, and controlled release. They also possess numerous functional groups on their surface, providing multiple sites for drug encapsulation or conjugation. This high density of functional groups enables dendrimers to carry a large amount of drug molecules, resulting in high drug-loading capacities. The release mechanism can be optimized by modifying the dendrimer structure or incorporating stimuli-responsive components, the release kinetics of encapsulated drugs can be controlled. This enables precise and sustained drug release over time or in response to specific triggers such as pH, temperature, or enzymatic activity [11].

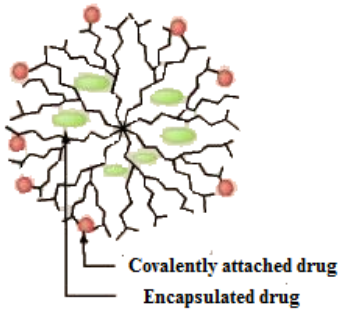

Fig. 4: Dendrimer Nanocarrier

2.5 Silica Materials

Silica-based nanocarriers can be synthesized in various forms, such as mesoporous silica nanoparticles, silica nanospheres, or silica-coated nanoparticles. Silica nanocarriers often possess a high surface area and ordered mesoporous structures. These properties allow for efficient drug loading and storage within the nanopores, providing a large drug-carrying capacity. The porous nature of silica nanocarriers enables controlled drug release kinetics. The release rate can be modulated by adjusting factors such as pore size, pore volume, surface modification, or encapsulation strategies. This control allows for

sustained and targeted drug release over time. Silica is generally considered biocompatible and has a low toxicity profile [12]. However, it's important to carefully engineer and characterize silica nanocarriers to ensure their safety and minimize potential adverse effects. Surface modifications and coatings can be employed to improve biocompatibility and reduce potential cytotoxicity. It's worth noting that the surface properties, pore size, and structural characteristics of silica nanocarriers can be tailored based on specific applications and desired drug delivery requirements. Phenytoin, doxorubicin, cisplatin, metronidazole, nifedipine, diclofenac, and heparin are examples of drugs which have been loaded into xerogels using this technique [1].

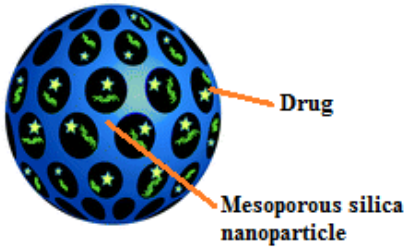

Fig. 5: Silica Nanoparticle

2.6 Carbon Nanomaterials

Carbon nanomaterials, such as carbon nanotubes (CNTs), graphene, and fullerenes, have gained significant attention as potential nanocarriers in various fields, including drug delivery, gene therapy, and imaging. Carbon nanomaterials can be used as nanocarriers for targeted drug delivery. Functionalized CNTs or graphene can be loaded with drugs, and their unique properties, such as high surface area, good biocompatibility, and the ability to penetrate cellular membranes, make them suitable for efficient drug delivery. Additionally, their optical properties allow for imaging and tracking of drug release. Carbon nanomaterials can act as imaging agents by incorporating contrast agents into their structure. For example, functionalized CNTs or graphene can be loaded with fluorescent dyes or magnetic nanoparticles to enable imaging of biological tissues and cells. Their high stability and unique optical and magnetic properties make them suitable for various imaging techniques, including fluorescence imaging and magnetic resonance imaging (MRI).

However, it is important to note that while carbon nanomaterials offer significant potential as nanocarriers, there are still challenges that need to be addressed, including biocompatibility, long-term safety, and scalability of production. Extensive research is being conducted to overcome these hurdles and optimize the use of carbon nanomaterials as nanocarriers in various applications.

The different ways by which a drug can be attached to carbon nanocarriers are adsorption, encapsulation in the carbon nanotubes or in the spaces between the nanotubes and attachment of active agents to functionalized carbon nanotubes.

Encapsulation has the advantage over the two remaining methods as the drug is protected from degradation during its transport to the cells and is released only in specific conditions. Drug release from carbon nanotubes can be electrically or chemically controlled [13].

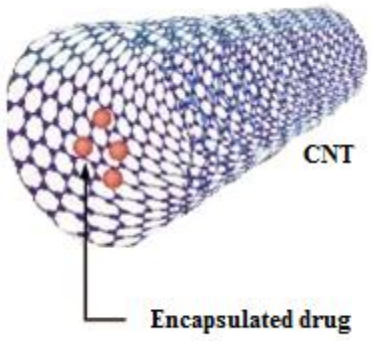

Fig. 6: Carbon Nanotube

2.7 Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) have emerged as promising drug carriers due to their unique magnetic properties and potential for targeted drug delivery. The MNPs can be guided to specific target sites within the body using external magnetic fields. By functionalizing the MNPs with specific ligands or antibodies that have affinity for target cells or tissues, they can be directed to the desired location. This magnetic targeting approach improves the localization of drug delivery, reducing potential off-target effects and improving therapeutic outcomes. The MNPs can be loaded with drugs, either by adsorption onto the particle surface or by encapsulation within the nanoparticle structure. The drug release can be controlled by various mechanisms, such as pH or temperature changes, enzymatic triggers, or the application of an alternating magnetic field. This enables the precise and controlled release of drugs at the target site, enhancing therapeutic efficacy and minimizing side effects. One crucial aspect of using MNPs as drug carriers is ensuring their biocompatibility and safety. Extensive research is being conducted to develop MNPs with appropriate surface coatings to minimize toxicity, improve stability, and prevent non-specific interactions with biological systems. Rigorous testing is essential to evaluate the biocompatibility and long-term safety of MNPs before their clinical translation. Overall, magnetic nanoparticles offer unique advantages as drug carriers, including targeted delivery, controlled release, imaging capabilities, and potential for combination therapies. While there are still challenges to address, ongoing research and development aim to optimize the design and functionality of MNPs for efficient and safe drug delivery applications. Another problem associated with inappropriate features of magnetic nanoparticles or inadequate magnet system, like they tend to aggregate into larger clusters loosing the specific properties connected with their

small dimensions and making physical handling difficult. In turn, magnetic force may not be strong enough to overcome the force of blood flow and to accumulate magnetic drugs only at target site [14]. Therefore, designing magnetic drug delivery systems requires taking into consideration many factors, e.g., magnetic properties and size of particles, strength of magnetic field, drug loading capacity, the place of accessibility of target tissue, or the rate of blood flow. Connecting a drug with MNP may be achieved by covalent binding, electrostatic interactions, adsorption, or encapsulation process [1].

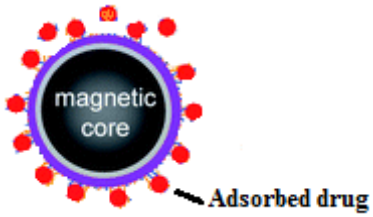

Fig. 7: Magnetic Nanoparticle

3 Chemotherapeutic Drugs for Cancer Treatment

Chemotherapeutic drugs are medications used to treat cancer by targeting and destroying cancer cells. They can be administered orally, intravenously, or through other routes depending on the specific drug and cancer type. Alkylating agents work by directly damaging the DNA of cancer cells, preventing them from dividing and growing. Examples include cyclophosphamide, cisplatin, and temozolomide. Antimetabolites are the drugs that interfere with the DNA and RNA synthesis of cancer cells by mimicking essential molecules needed for cell replication. Examples include methotrexate, 5-fluorouracil, and gemcitabine. Anthracyclines drugs are derived from natural sources and interfere with the DNA of cancer cells, preventing cell replication. They are commonly used for treating breast cancer and include drugs such as doxorubicin and epirubicin. Topoisomerase inhibitors target enzymes called topoisomerases that help in the replication and transcription of DNA. By inhibiting these enzymes, the drugs interfere with DNA synthesis and cause cell death. Examples include etoposide and irinotecan. While the mitotic inhibitors drugs disrupt the process of cell division by affecting the microtubules that help in chromosome separation during cell division. Examples include paclitaxel, docetaxel, and vinblastine. Hormone therapy is used to treat cancers that are hormone-sensitive, such as breast and prostate cancer. It works by blocking or interfering with the hormones that promote cancer growth. Examples include tamoxifen, letrozole, and leuprolide. Targeted therapies use the drugs that specifically target certain molecules or pathways involved in cancer growth and survival. They are designed to be more selective in targeting cancer cells and may have fewer side effects compared to traditional chemotherapy. Examples include trastuzumab, imatinib, and rituximab. It's important to note that the selection of chemotherapy drugs depends on the specific type and stage of cancer, as well as individual patient factors. Treatment plans are often tailored to the

patient's condition to achieve the best possible outcomes while minimizing side effects [4, 15].

4. Proposed Model for Magnetic Drug Targeting Using Magnetic Nanoparticles

Smart drug delivery systems refer to advanced technologies and techniques designed to improve the effectiveness, efficiency, and safety of drug delivery to the target site in the body. These systems incorporate various components, such as sensors, actuators, and control mechanisms, to achieve controlled and targeted drug release. In the current model we have tried to propose an ideal system for smart drug delivery system (SDDS) using functionalized semiconductor-magnetic nanocomposites in a core-shell form and doping either core or shell with some impurity. Where the magnetic core will be used for guiding the drug to the affected area with the help of external magnetic field. While the semiconductor core either in pure form or doped with some impurity can be used for imaging and monitoring therefore. Te doping will enhance te properties of the existing structure rather than inducing new property/ies. On such a functionalized nanomaterials a suitable drug can be loaded and drugs can be released in a controlled manner. These particles can respond to specific stimuli such as temperature, pH, or enzymes, enabling triggered drug release at the desired site. The SDDS will have several advantages compared to conventional drug delivery systems. The conventional controlled release systems are based on the predetermined drug release rate irrespective of the environmental condition at the time of application. On the other hand, SDDS is based on the release-on-demand strategy, allowing a drug carrier to liberate a therapeutic drug only when it is required in response to a specific stimulation. The best example of SDDS has been self-regulated insulin delivery systems that can respond to changes in the environmental glucose level [16,17].

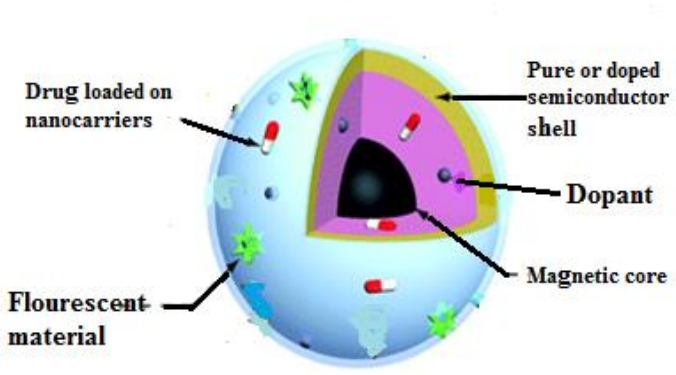

Fig. 8: Advanced generation nanoparticle as SDDS

Conclusion

In conclusion, the field of drug delivery systems has made significant advancements in recent years, leading to enhanced efficiency and targeted therapeutics. These advancements have revolutionized the way drugs are administered, enabling precise delivery to specific tissues or cells while minimizing systemic side effects. By overcoming various biological barriers and optimizing drug formulations, researchers have been able to improve drug bioavailability, stability, and release kinetics. One notable advancement in drug delivery systems is the development of nanotechnology-based approaches. Nanoparticles, liposomes, and other nano-sized carriers have been extensively studied and engineered to encapsulate drugs and deliver them to their intended targets. These nanostructures offer advantages such as prolonged circulation time, improved tissue penetration, and controlled drug release, making them ideal candidates for targeted therapeutics.

Furthermore, the integration of smart and stimuli-responsive drug delivery systems has allowed for on-demand drug release at specific sites. These systems can be triggered by external stimuli such as light, heat, pH changes, or specific enzymes, providing spatial and temporal control over drug delivery. This targeted approach not only increases therapeutic efficacy but also reduces off-target effects, improving patient outcomes and safety.

Overall, the advances in drug delivery systems have brought us closer to personalized medicine and tailored therapies. By enabling targeted delivery of drugs to specific sites and optimizing their pharmacokinetics, these advancements hold tremendous potential for enhancing therapeutic outcomes, reducing drug resistance, and improving patient quality of life. Continued research and collaboration across various disciplines will further refine these systems, ultimately transforming the landscape of drug delivery and patient care.

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