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Smart Nanocarrier Based Drug Delivery Systems

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A B S T R A C T

One area of medicine with numerous therapeutic uses is nanomedicine. Medication delivery research at the nanoscale must be conducted as nanocarriers using active or passive targeting strategies for cell-specific medication delivery. Nanocarriers that have been shown to be too intelligent as a nano-based drug delivery method include liposomes, solid-lipid nanoparticles, dendrimers, polymeric nanoparticles, mesoporous silica nanoparticles, inorganic nanoparticles, nanotubes, quantum dots, and nanofibres. The nanoparticulate system exhibits great stability, high specificity, high efficacy, and the capacity to administer both hydrophilic and hydrophobic medications in a variety of dosages and via a variety of routes. Nanoparticulate systems are demonstrating widespread use in biomedical applications and nanomedicines to treat illness. Nonspecific distribution and controlled release of drugs in conventional drug delivery system have led to the development of smart nanocarrier based drug delivery system, which are also known as smart drug delivery system (SDDS). SDDS can deliver drugs to target site with reduced dosage frequency and in a spatially controlled manner to mitigate the side effects experienced in controlled drug delivery system. Smart nano carrier, nanoparticles used to carry drugs are at the focus of smart drug delivery system. This review highlights the importance of smart nano carriers including liposomes, dendrimers, polymeric nano particles, quantum dots, nanotubes etc. The nanocarriers are described in terms of their features and its application in drug delivery.

Keywords: Nanoparticles, Liposomes, Dendrimers, Polymeric nanoparticles, Quantum dots, Nanofibres

INTRODUCTION

By boosting the drug's concentration, length of residence in target cells, and reducing adverse effects, drug delivery systems (DDSs) have the potential to improve the therapeutic index of medications. Through improved drug pharmacokinetics, biodistribution, and activity as drug reservoirs, DDSs improve the pharmacological characteristics of free medicines and mask their negative qualities by delivering the potentially active drug to the site of action nano vehicle. The typical size of these nanoparticles varied depending on their intended use, ranging from a few nanometers to several hundred nanometers. A variety of natural, organic, and inorganic materials, such as ceramic, polymers, metals, and lipids, are utilized to produce nanoparticles, such as liposomes and micelles. Entrapment and other physical interactions are the primary means by which therapeutic medicines are integrated into the nanoparticles. Because drug delivery systems (DDSs) increase drug concentration, residence time in target cells, and minimize adverse effects, they have the potential to improve the therapeutic index of medications. By using a nano vehicle to transport the potentially active drug to the site of action, DDSs improve the pharmacological characteristics of free medicines and mask their unfavorable aspects by enhancing drug pharmacokinetics, biodistribution, and action as drug reservoirs. A few nanometers to several hundred nanometers, depending on the intended use, were typically the size range of these nanoparticles. Metals, ceramics, polymers, and lipids are among the several natural, organic, and inorganic materials that are utilized to make nanoparticles, such as liposomes and micelles. Entrapment is one of the primary physical interactions that incorporate therapeutic medicines into the nanoparticles.

Nanotechnology provides opportunities and possibilities for the development of a novel drug delivery system. It acts as the bridge between biological and physical sciences. The development of nanoparticles using novel drug delivery system has attracted a high level of interest due to various advantages over the conventional drug delivery system. Using novel drug delivery approaches development of therapeutically effective pharmaceutical products become easy. Using novel drug delivery approaches following can be achieved easily;

- Enhance the delivery of hydrophobic as well as hydrophilic drug.
- Delivery of macromolecular sized drugs to intracellular sites becomes easy.
- Target specific delivery can be achieved.

Delivery of more than one drug at a specific time through a single dose of drug can also be achieved.

SMART NANO BASED DRUG DELIVERY SYSTEM

A smart nano-based drug delivery system is a technique that use materials at the nanoscale to carefully distribute therapeutic chemicals to predetermined target locations. These systems improve the effectiveness of drug delivery by raising the concentration of medication in specific body areas relative to others.

Advantages of smart nano-based drug delivery

- Minimization of drug degradation and loss
- Prevention of adverse effects of drugs
- Reduction of dosing frequency
- Improved drug utilization
- Sustained or controlled release
- Increased bioavailability
- Uniform dosing of drugs

Different types of nanoparticles used in drug delivery

Nanoparticle on the basis of integrity, are classified as rigid nano particles and non-rigid nano particles. Rigid nanoparticle shows more significant mechanical strength as compared to non-rigid nanoparticles, i.e., polymeric nanoparticles, carbon nanotubes etc. Liposomes and solid nanoparticles are categorized under non-rigid nanoparticles. They are also classified on the basis of dimensions such as one-dimension(1D), two-dimensions(2D), and three-dimensions(3D). One- dimensional systems such as thin film or fibres,are using in different technologies like fiber-optic systems, information storage systems, magneto-optic and optical devices. Nowadays nanofibres are attracting interest due to their specific targeting to the cell. Carbon nanotubes (CNTs) are example of two-dimensional nanoparticles.

NANO-BASED DRUG DELIVERY SYSTEM

LIPOSOMES

The Greek terms lipo and soma—lipo meaning fat and soma meaning body are the origin of the word liposome. Fat body which is composed of phospholipid. Lipid molecules consist of head and tail that means hydrophobic and hydrophilic. They are small artificial vesicles of spherical shape that can be created from cholesterol and non-toxic phospholipid. Due to their size and hydrophilic character, they are promising system for drug delivery. They are spherical shape with particle size ranging from 30nm to several micrometers. They consist of one or more lipid bilayer surrounding aqueous units, where polar head are oriented in the pathway of interior and exterior aqueous phase. Liposome can trap both hydrophilic and hydrophobic compounds, avoid decomposition of entrapped combination and release the entrapped at designated targets.

Liposomal Encapsulation Technology is the newest technique to transmit drug. This form of drug delivery system proposal targeted the delivery of vital combination to body.

Methods involved in liposomal preparation consist of following steps:

- Drying of lipid from organic phase.
- Dispersing lipid in aqueous phase
- Purifying resultant liposome and analyzing the final product.

Conventional technique used for small scale application; it is not convenient foe large scale application. It has disadvantage that continuous contact of lipid/drug with organic phase, abnormal size distribution and sterilization of lipid is difficult due to temperature sensitive nature of lipids. So novel techniques are used today.

APPLICATIONS

Medicine and pharmacology: Application of liposomes can be divided into diagnostic and therapeutic application of liposome containing various markers or drug. Advances in liposome design are leading to new application for delivery of new biotechnological products. Liposomal formulation of all-trans retinoic acid and daunorubicin which has received food and drug administration consent as a first line treatment of AIDS related advance Kaposi's sarcoma.

Liposome in parasitic diseases/ infections: Leishmaniasis is a parasitic infection of macrophages. Liposome accumulate in the very cell population which is infected and so an ideal drug delivery vehicle was proposed, liposome as carrier for amphotericin B in antifungal therapies. This is the drug of choice

in dispersed fungal infection which often work with chemotherapy, immune system or AIDS. Liposomal encapsulation inhibits the accumulation of drug in these organs and reduce toxicity.

Liposome as drug delivery vehicle in cancer immunotherapy: Liposome are lipid-based nanoparticles with high potential to improve cancer immunotherapies, since they can incorporate a high variety of cancer drug molecules (e.g., peptides, proteins, antibodies). The application of liposomal-based drug delivery systems in immunotherapy can be categorized into five groups:

(1) Immunization: the coordinated delivery of antigens via liposomes and other stimulatory molecules to APCs or cells.

(2) Tumor normalization: overcoming tumor-driven immunosuppressive signals in the TME by liposomes to improve selectivity and decrease systemic toxicity.

(3) Tumor modulation: correcting or modulating an existing development of anti-tumor response.

(4) Tumor targeting: targeting overexpressed surface molecules on cancer cells.

(5) Combinational therapy: exploring the combinational strategy between immunotherapy and others.

DENDRIMERS

Nanosized, radially symmetric molecules with well-defined homogenous and monodisperse structure that has a typically symmetric core, an inner shell and an outer shell. Structure of dendrimer comprised of 3 parts: The multivalent surface which contain very reactive sites, outer shell presented below multivalent surface, core which is highly protected by branches of high generation dendrimer. Multivalent high generation dendrimers are synthetic polymeric macromolecules which contain group of branched monomers. Cationic dendrimer like polyamido amines, poly-L-lysine, poly (propylene amine), among this polyamido amines are widely used.

Dendrimer can be utilized as suitable carrier for drug delivery by approaching two different ways: (1) Active agents embedded inside the dendritic body. (2) Ligand-based drug dendrimer interaction or drug covalently bound to active dendrite sites. Synthesis of dendrimer can be done by 3 methods:

- Divergent Method: Firstly, the core part is synthesized followed by addition of other functional groups or build blocks one by one to give star like branches of dendrimers.
- Convergent Method: It is opposite to above, in this synthesis starts from outside surface to give specific molecular structure to branches.
- Double exponential and mixed method: Two principal polymer or monomer interact for development of both divergent and convergent and provide trimer.

APPLICATIONS

Dendrimers in biomedical field: The dendritic polymers are analogous to proteins, enzymes and virus and are easily functionalized. Liposomes and other molecules can either be encapsulated in their interior voids. Modern medicines use a variety of this material as potential blood substitutes

Dendrimer are used as anticancer drugs

Dendrimer in drug delivery: Host guest properties of dendritic polymers are currently under scientific investigation and have gained critical position in field of supramolecular chemistry.

Dendrimers are used as magnetic resonance imaging contrast agent: Dendrimer- based metal chelates act as MRI contrast agent.

Dendrimer are used for enhancing solubility: PAMAM dendrimers have potential for solubility enhancement. They enhance the bioavailability of drugs that are poorly soluble and substrate for efflux transporters.

POLYMERIC NANOPARTICLES

Polymeric Nanoparticles are colloidal systems having size range between 1-300nm having variety of compounds, including polymers and lipids along with active pharmaceutical ingredient. They are stable with a high loading of many agents as well as high control over drug release kinetics. Polymers are divided into two classes like natural and synthetic. Polymers like polylactic acid, polyglycolic acid, polyanhydrides etc are examples of synthetic polymer used as drug delivery system to encapsulate a variety of therapeutic compounds. Apart from this natural polymer are also used such as chitosan ,gelatin etc. Biodegradable polymers are widely used due to their biocompatibility, nontoxicity and easy degradable quality.

Lipid polymer hybrid nanoparticles are used in a novel drug delivery system to overcome the limitation associated with polymeric nanoparticles. Polymeric nanoparticles are divided into two: Nanospheres and Nanocapsules. Two approaches are used for the preparation of polymeric nanoparticles

- Top-down approach: The preformed polymer is used for formation of polymeric nanoparticles.
- Bottom-up approach: Polymerization of polymer results in formation of polymeric nanoparticles.

The major function of polymeric nanoparticles is to deliver the pharmaceutical agent to specific site of action, achieving a high concentration of drugs and effectiveness and efficacy of drug. These characteristics make them a point of interest for delivery of drug, protein or genes. Thus, they are used in anticancer therapy, vaccine and gene therapy.

APPLICATIONS

Polymeric Nanoparticles for cancer therapy: The general concept of all nanomedicine for cancer application, but most notably for polymeric formulation is the incorporation of active pharmaceutical ingredient which can be encapsulated within a nanoparticle and delivered directly to mitigating side effects and enhance therapeutic efficiency..

Polymeric nanoparticle for immune engineering: Research in polymeric nanoparticles involving controlling immune regions by tailoring interaction between immune cells and NPs, due to their inherent size, nanoparticles are naturally internalized by phagocytic antigen-presenting cells. Antigen presenting cells are responsible for internalizing foreign particulate and driving adaptive immune response to combat infection.

Polymeric nanoparticles for pulmonary diseases: Historically, large porous polymer particles have been successful in pulmonary drug delivery. Using biodegradable polymers such as PLGA, these LPP lead to advent of inhalable insulin with sustained release in lungs. Polymeric nanoparticles have been developed to deliver a wide range of payload for pulmonary application including vaccines, insulin, antibiotics.

MESOPOROUS SILICA PARTICLES

Mesoporous silica nanoparticles are silica particles with ordered mesopores having uniform pore size. Nowadays this drug delivery system is being utilized for loading different cargoes ranging from drug to macromolecules, due to its advantageous properties like uniform pore, tunable size, internal as well as external pores that are opened through gating mechanism make it a distinctive drug carrier and easy functionalisation of surface. Mesoporous silica particles are potential drug carriers with following features:

- Homogenous in size and for fine control of drug load and release kinetics that is due to the ordered pore network.
- High pore volume than the required number of pharmaceuticals.
- High potential for drug absorption due to high surface area.
- Better control over drug loading and release kinetics, as they contain silanol groups on surface.

These features make it a good candidate for drug delivery system. Mesoporous silica nanoparticles show greater difference in biopharmaceutical attributes of different shapes. Spheres and rod shaped are widely used. Higher drug loading capacity, high compatibility and overall kinetic properties are shown by rod shaped particles. For the synthesis of mesoporous silica nanoparticles surfactant: non-ionic, cationic or amphilic), silicon source and cosolvent are used.

APPLICATIONS

Drug delivery: Mesoporous silica nanoparticles are ideal nanocarriers for storing, safeguarding, and delivering medication to intended location. By adding a target agent to the surface of mesoporous silica nanoparticles, one can direct the agent to precise injured tissues while minimizing undesirable side effects. Cancer target therapy is the main focus of study of mesoporous silica nanoparticles for drug delivery

Cell imaging agent: Mesoporous silica nanoparticles are used for biomedical imaging and diagnostic application. Due to its hydrophilic surface and ability to be easily distributed in aqueous solution, used as imaging agent.

Target specific in tumor: Mesoporous silica nanoparticles can be used in cancer therapy to enhance specific binding to receptors of target cells or tissues while decreasing non- specific binding to those same receptor. The development and spread of cancer can be prevented by targeting specific molecules involved in tumor progression or indirectly by using target- specific mesoporous silica nanoparticles to activate the immune system to recognize and destroy cancerous cells.

Biosensing and cell tracing: Mesoporous silica nanoparticles are used as sensor devices for in vivo and invitro detection of target within individual cells. Due to their size and adaptable composition, they are used as biosensing element

SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles consist of solid lipid matrix, surfactant and sometimes co-surfactant. Solid matrix consisting of core is coated with phospholipid. Solid core matrix is hydrophobic in nature as well as hydrophobic tail region of phospholipid lodge into core matrix. Solid lipid nanoparticles are less toxic and biocompatible as compared to other nanoparticles. It shows high drug protection, good physical stability, biocompatibility and ease of preparation. Another for the rapid growth of solid lipid nanoparticles was its nature to deliver lipophilic and hydrophilic drug along with genes, peptides and oligonucleotides etc.

APPLICATIONS

Solid lipid nanoparticles for parenteral application: Solid lipid nanoparticles are very suitable for drug delivery because they consist of well tolerated ingredients and have good storage capabilities after lyophilization and sterilization. Solid lipid nanoparticles have been used for viral and non-viral gene delivery. They have potential benefits in targeted gene therapy in treatment of cancer.

Solid lipid nanoparticles for respiratory application: Solid lipid nanoparticles can be proposed as carrier of anticancer drugs in lung cancer treatment or peptide drugs to improve bioavailability. Nebulization of solid lipid nanoparticles carrying antitubercular drugs was observed to be successful in improving drug bioavailability and reduce dosage frequency for better management of pulmonary tuberculosis.

For ocular application: Biocompatibility and mucoadhesive properties of solid lipid nanoparticles improve interaction with ocular mucosa and prolong corneal residence time of drug. Pilocarpine delivery via solid lipid nanoparticles were commonly used for glaucoma treatment.

For cancer chemotherapy: Tamoxifen an anticancer drug has been incorporated in solid lipid nanoparticles to prolong release of drug. Metaxantrone solid lipid nanoparticle injection was formulated to reduce toxicity and improve safety and bio efficacy of drug in treating breast cancer and lymph node metastases.

NANOPARTICLES COMPRISING OF INORGANIC COMPOSITE

Nanoparticles comprising inorganic composites are materials that combine nanoparticles of inorganic substances, often designed to improve properties of individual components. These composite nanoparticles usually consist of a core material (like metal, metal oxides or ceramics and a shell or surface modification.

Gold and silver nanoparticles are widely used because of their persistent vigorous catalytic activity and bactericidal activity. Due to effective oscillation of electrons, gold and silver nanoparticles have surface Plasmon due to which broader electric field was generated and excellent optical properties were observed. Antifungal activity of alginate-CuO bio composite was found to be effective against Aspergillus Niger hence it is used in various biomedical applications. Prepared gold nanorods and Fe_3O_4 superparamagnetic composite nanoparticles were sensitive to near IR laser which helped in wound healing.

APPLICATIONS

Drug delivery: Gold nanoparticles can be used to deliver drug in targeted manner, minimizing side effects and improve therapeutic efficiency. They can be functionalized with various molecules like antibody, peptides etc for targeted drug delivery.

Cancer therapy: They are used in photothermal therapy, where they absorb light and convert it into heat which selectively kills cancerous cells.

Sensors and Biosensors: They are widely used in the development of highly sensitive sensors for detecting pathogens, toxins etc. They are also incorporated into biosensors for detecting biological markers, offering high sensitivity and selectivity.

Catalysts: Gold nanoparticles serve as catalysts in various chemical reaction due to their high surface area to volume ratio and ability to facilitate reactions under mild conditions.

NANOTUBES

Nanotubes have a very high range of electrical conductivity. Mainly classified into two types: fullerenes and carbon nanotubes. Fullerenes are made up of 60 carbon atoms used for targeting the active pharmaceutical ingredient, but they have some limitations which can be overcome by carbon nanotubes. The process of formation of carbon nanotubes are classified into 2 types:

1. Single walled nanotubes
2. Multiwalled nanotubes. Multiwalled nanotubes are made up of concentric cylinder that is around hollow central cylinder. Single walled nanotubes are a single layer of cylinder. Carbon nanotubes are found to be low cytotoxic and more biocompatible. Cell viability assay indicate that single walled nanotubes hybrid showed lower toxicity towards normal HEK293 hybrid cell lines. Single walled nanotubes-based drug carrier was a promising approach for cancer therapy. Developed multilayer nanotubes were investigated for killing of cancerous cells and found to have potent therapeutic agent for the remote killing of tumor cells.

APPLICATIONS

Targeted drug delivery: Carbon nanotubes can be functionalized with anticancer drugs, antibodies or peptides that target specific cancerous cells. They are the potent carriers for drug delivery system. They can be used to deliver genetic material such as RNA or DNA into cancerous cells.

Functionalized carbon nanotubes are used as contrast agent in imaging techniques like MRI or CT, aid in early detection and monitoring of tumors.

Artificial implants: They are used as implants in the form of artificial joints without host reaction. Carbon nanotubes act as bone replacement because of their tensile strength.

QUANTUM DOTS

Quantum dots are also named nanoscale semiconductor crystals and they exhibit optical, fluorescent and electronic properties. Quantum dots are widely used in biomedical imaging but quantum dots are now also used as nano sensors for diagnosing cancerous and stem cells imaging in regenerative medicine. Numerous quantum dots are present which are polymer dots, graphene quantum dots, carbon quantum dots. Carbon quantum dots are also termed as carbon dots. They were found to be cost effective and easy to synthesize. Graphene quantum dots were used as a loading carrier for cytarabine and then encapsulated into chitosan. Quantum dots were promising delivery system and are used as a venue for the development of smart and controlled release system with natural polysaccharides and other polymers.

APPLICATIONS

Liver cell imaging and in vivo imaging: On cellular level, Quantum dots are used for visualization of intracellular component. They are used to visualize different organs and tissues in vivo after administering quantum dots functionalized with specific ligands to enhance their affinity for those organs or tissues.

Photodynamic Therapy: Quantum dots have the ability to act both as photosensitizers, energy donors or other photosensitizers. Quantum dots have numerous advantages compared to organic photosensitizers including potent light absorption, strong emission, high photostability, water solubility etc. In addition, size and composition of quantum dots can be manipulated to optimize emission in near IR region which demonstrate strong tissue penetration that is suitable for treatment of deep sited tumors.

Biosensors: Quantum dots are used in a wide variety of diagnostic, toxicological, and follow up medical application. Quantum dots are used in environmental application such as detection of water and soil contamination etc.

NANOFIBERS

Nanofibres are fine solid fibres synthesized using electrostatic forces. They are found to be biocompatible and can be administered through any route of administration. It can deliver the drug to target without drug release prior to destination. It has also been used in wound dressing, enzyme immobilization, and tissue engineering. Electrospun nanofibers are extremely long and are made through the process of electrospinning. Electrospinning process involves four main components: (1) Base (2) Spray (3) Jet (4) Collector. In electrospinning, when an electric voltage is applied between two electrodes, droplets of liquid are at the end of the so-called Taylor cone. Electric field is applied that leads to the occurrence of charge on solution held by alteration of surface tension and further increment of electric field leads to elongation of solution to form conical shape called Taylor cone.

APPLICATIONS

Medical application: Functionalized nanofibers can be engineered to deliver drug to specific tissue or cells minimizing side effects and improve therapeutic efficiency. Nanofibers can be used to deliver chemotherapy drugs directly to cancerous cells improving targeting of tumors and reduce side effects.

Tissue engineering: They are employed in the creation of scaffolds for the regeneration of skin, bone, cartilage or nerve tissue.

Biosensing and imaging: Nanofibers can be integrated into biosensors for detecting pathogens, biomolecules or environmental pollutants. They improve the detection of particular tissues or abnormalities in MRI or CT images by acting as a contrast agent.

NANOMEDICINE FORMULATIONS

In recent years both broadening in nanocarrier typology and the increase in complexity of particles and materials employed have inspired exploration for new delivery system and brought about various products as well as numerous clinical trials for biotechnology and nanomedicine application. However, before premarket authorization, they are subjected to a range of preclinical and clinical validation by regulatory agencies such as European Medicine Agency and FDA. Among organic nanomedicines approved for use on market, it is useful to distinguish between two main categories: polymer based and lipid-based nanoparticles. The degradable hydrophobic polymers like PLA, PLGA etc are the most promising polymer system for the development of nanomedicines.

Some of the relevant polymer based and lipid-based nanomedicines approved by FDA

Table 1: Polymer based nanomedicines

Clinical products	**Formulation**	**Indication**
Renagel	Poly (allylamine hydrochloride)	Chronic kidney disease
Eligard	Leuprolide acetate and polymer PLGA	Prostate cancer
Cimzia/Certolizumab	PEGylated antibody fragment	Crohn’s disease/Rheumatoid arthritis

Table 2: Lipid based nanomedicines

Clinical products	Formulation	Indication
Doxil/Caelyx	Liposomal doxorubicin	Ovarian cancer, breast cancer, Kaposi's sarcoma
Daunoxome	Liposomal daunorubicin	AIDS related Kaposi sarcoma
Marqibo	Liposomal vincristine	Acute lymphoblastic leukemia

Liposomal formulation represents the most successful category of nanocarrier employed for drug delivery purposes. Anticancer drugs like doxorubicin, daunorubicin, paclitaxel and vincristine are among the most extensively drugs for liposomal formulation and are currently in clinical use in cancer therapy.

CONCLUSION

The primary goal of effective nanostructured delivery systems is to minimize the dosage of the medicine required to produce a particular therapeutic effect, which will reduce the expenses and adverse effects of its use. The two primary types of organic and inorganic nanostructured materials that are frequently used in drug delivery procedures offer a number of advantageous and complementary qualities that can be used to one's advantage. On the one hand, organic soft nanocarriers, including liposomes and amphiphilic polymers, offer superior characteristics that correspond to the physicochemical conditions found in healthy (and pathological) tissues, making them the best examples of biocompatible nanostructures. However, the hard nanoparticles made of inorganic materials (such mesoporous silica nanoparticles, quantum dots, and gold) offer complementing advantages for the diagnosis and identification of pathological states within sick tissues. Designing effective nanocarriers for particular purposes requires careful consideration of the properties of the nanocarriers, including size, shape, material substrate, and surface chemistry, since the microenvironment conditions in diseased tissues greatly affect the delivery efficiency of nanocarrier systems.

Although smart nano-DDSs have demonstrated greater efficacy in diagnosis and treatment, evaluation of their possible druggability is still necessary before they are introduced into clinical settings. Enhancing preclinical research of advanced DDSs to produce reliable and transferable output to clinical-trial success would be a huge challenge for researchers. However, it is important to remember that the ultimate goal of all our efforts is to treat patients. In order to guarantee that more stimulus-sensitive nanomedicine can be deployed in clinical settings, future research on smart DDSs for controlled drug delivery should concentrate on clinical translation.

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