Review Article

Developments in Drug Delivery with Special Reference to Nanotechnology – A Review

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ABSTRACT

With the emergence of nanoscience as a distinct speciality in recent times, various methods have been introduced in pharmaceuticals to produce drugs which are more efficacious and less hazardous.

Nanomedicine is an offshoot of nanotechnology, which deals with the employment of devices less than 200 nanometres in size, in various diagnostic and therapeutic procedures. Nanocarriers get concentrated preferentially in tumours, inflammatory sites, and at antigen sampling sites. Once accumulated at the target site, they can act as a local drug depot at the disease site. Nanomaterials comprise carbon-based particles, such as fullerenes, various organic dendrimers, liposomes, and other polymeric compounds. Quantom dots, nanotubes and nanoparticles, nanocapsules and nanospheres, nanoemulsions, nanosuspensions, and polymeric phospholipid micelles are a few that are being increasingly tried in the nano drug delivery system.

However, it is important to remember that nanoparticles can act on living cells at the nanolevel, producing not only biologically desirable, but also undesirable effects.

Key Words: Nanomedicine, Nanoparticle, Drug delivery, Carbon nanotube, Quantom dot, Fullerene, Dendrimer, Liposome, Phospholipid micelle

Introduction

Researchers have been harbouring for long to produce drugs with excellent tissue penetrability and good bioavailability, relatively nontoxic property, and with need only for lesser dosing with increased dosage intervals. In this review, an attempt is made to cover a majority of the new drug delivery systems with special focus on the nanoscience-based, target delivery systems.

The common oral dosage forms follow either a zero-order or first-order release, in which the drug is released at a substantially steady rate per unit of time. However, there are instances where maintaining a constant blood level of a drug is not desirable. In such cases, a pulsatile drug delivery may be more apt. These are of two types. One is a site-specific system, in which the drug is released at the desired site within the intestinal tract, and the other is a time-controlled device, in which the drug is released after a well-defined time period. Factors like pH or enzymes present in the intestinal tract control the release of target-delivered system, whereas the drug release from time-controlled systems is controlled primarily by the delivery system, and not by the environment.[1] The delayed liberation of orally administered drugs has been achieved through a range of formulation approaches, including single or multiple unit systems provided with release-controlling coatings, capsular devices, and osmotic pumps. It is worth mentioning that the utilization of mesoporous carriers diminished the pH dependency of ibuprofen, providing a solution for poorly soluble drug compounds.

Non-invasive methods including drug manipulation, drug transformation into lipophilic analogues, prodrugs, carrier-mediated drug delivery, receptor/vector mediated drug

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delivery and intranasal drug delivery, which exploits the olfactory and trigeminal neuronal pathways to deliver drugs to the brain, are also being widely used today.[2] Other novel methods include an implantable ocular drug delivery system, using wireless power transfer and communication system, to overcome the risks associated with battery failure and leakage of chemical from the battery, which are usually encountered in implantable systems. This is based on near-field inductive coupling, which triggers the release of drug within 5 seconds; such short exposure to RF radiation does not produce any adverse reaction.[3]

Parenteral formulations, especially IV preparations, possess the ability of direct access to the bloodstream, with rapid onset of drug action, and precise targeting of specific organs and tissue sites. Triglyceride emulsions, liposomes and micellar solutions are already in use, while recently developed parenteral lipid-based systems include nanoemulsions, nanosuspensions and polymeric phospholipid micelles.

Over a period of time, various methods have been introduced in pharmaceuticals to reduce drug toxicity, and in recent times, a new era has blossomed, with the invention of nanomaterials. There are a variety of such nanomaterials in use today. Nanocapsules are vesicular systems in which a drug is confined to a cavity surrounded by a polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm.[4] However, particles that are more than 200 nm in size are not heavily pursued, and nanomedicine often refers to devices less than 200 nm (i.e., the width of microcapillaries). Typically, the drug of interest is dissolved, entrapped, adsorbed, attached and/or encapsulated into or onto a nano-matrix. These nanoparticles possess different properties and release characteristics for the best delivery or encapsulation of the therapeutic agent.[5-7]

Developments in the field of nanotechnology provide opportunities to characterize, manipulate, and organize matter systematically at the nanometer scale. Biomaterials with nanoscale organizations are being used as controlled-release reservoirs for drug delivery, and artificial matrices for tissue engineering. Drug-delivery systems can be synthesized with controlled composition, shape, size and morphology. Their surface properties can be manipulated to increase solubility, immunocompatibility and cellular uptake. Most studies on nanoparticles deal with microparticles created from polylactic acid (PLA), polyglycolide (PLG), and polylactide-co-glycolide (PLGA).[8] XP-clad nanoparticles that represent a novel formulation method, uses planetary ball milling to generate particles of uniform size with 100% loading efficiency of hydrophobic or hydrophilic drugs, and subsequent coating for targeted delivery. However, electrical, optical, thermal, and other properties of these materials may undergo change, which arise from the behaviour of its surface atoms, and also, squeezing the atom's electrons into smaller-than-typical spaces can change properties such as the colour of the light they emit, and their chemical reactivity. Therefore, nanoparticles can act on living cells at the nanolevel resulting not only in biologically desirable, but also in undesirable effects. Nano controlled-release systems not only target specific sites in the human body but also can penetrate the cell membrane for gene, nucleic acid and bioactive peptide.

Nanoparticles determine the in vivo distribution, biological fate, toxicity, and targeting ability of drug delivery systems. Solubility, diffusion, and biodegradation of the particle matrix govern the release process. In the case of nanospheres, drug release occurs by diffusion or erosion of the matrix. If the diffusion of the drug is faster than matrix erosion, then the mechanism of release is largely controlled by a diffusion process. The rapid initial release or 'burst' is mainly attributed to weakly bound or adsorbed drug to the relatively large surface of nanoparticles. In addition, they can influence drug loading, drug release, and stability of drugs.[10] Many studies have demonstrated that nanoparticles have a number of advantages over microparticles.[11] Generally, nanoparticles have relatively high cell uptake when compared to microparticles. Their superiority over conventional medicines lies in their extremely small size. Particle size has effect on t1/2 lifetime and pattern of deposition.[12] This allows drugs of nanosize to be used in much lower concentrations.[13]

Recently, a nanoparticle insulin delivery system was prepared by interaction of dextran sulfate and chitosan in aqueous solution. This product greatly enhances the controlled release of insulin, and is pH-sensitive. It also maintains its immunogenic bioactivity with improved bioavailability of its oral delivery. Cholesterol nanoparticles have been developed that stimulate the immune system, and are readily taken up by dendritic

cells. Curcumin, known to have anti-cancer properties has been of limited use due to its poor solubility and minimal systemic bioavailability. This has been resolved by encapsulating curcumin in a polymeric nanoparticle, creating "nanocurcumin". Nanocurcumin provides an opportunity to expand the clinical repertoire of this efficacious agent by enabling soluble dispersion.[14]

Target delivery is the most important step in the reduction of drug toxicity. Targeting consists of two methods Active targeting is achieved by conjugating the therapeutic agent or carrier system to a tissue or cell-specific ligand.[15] Passive targeting is achieved by incorporating the therapeutic agent into a macromolecule or nanoparticle that passively reaches the target organ. Drugs encapsulated in nanoparticles or drugs coupled to macromolecules can passively target tumours through the enhanced permeability and retention (EPR) effect. Alternatively, catheters could be used to infuse nanoparticles to the target organ or tissues. For example, localized delivery of drug-bearing nanoparticles to sites of vascular re-stenosis may be useful for providing sustained drug release at specific sites on the arterial wall.[16]

Such promising and versatile nanodrug delivery systems therefore include nanoparticles, nanocapsules, nanotubes, nanogels, etc.[17] Increasingly employed nanomaterials include pure carbon-based particles such as fullerenes, various organic dendrimers, liposomes, and other polymeric compounds. Studies have shown that heparinization can significantly enhance the blood compatibility of nanomaterials.[18] These vehicles have been incorporated with antibodies and peptides, which interact with cell-surface tumour antigens. Once targeted, these new nanomaterials can then deliver radioisotopes or its generators to the cancer cells.

Indeed, the focus of nanotherapy has gradually shifted from passive targeting systems (e.g., micelles), to active targeting. Super paramagnetic iron oxide particles can be used in conjunction with magnetic resonance imaging (MRI) to localize the tumour, as well as for subsequent thermal ablation. This has been used, for example, to target glioblastoma multiforme (GBM), a primary malignant tumour of the brain with few effective therapeutic options. Direct intracranial drug delivery by intracerebroventricular, intracerebral or intrathecal administration, after creating reversible openings in the head, are successfully being used.[19] It is well known that one of the most difficult malignancies to detect and treat is brain cancer. Anticancer drugs such as doxorubicin and loperamide bound to nanomaterials have been shown to cross the intact blood-brain barrier and release at therapeutic concentrations in the brain. Nanoparticles can cross the blood-brain barrier following the opening of endothelium tight junctions by hyper-osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumours.[20]

Tumour targeting single-walled carbon nanotubes (SWCNT) have also recently been synthesized.[21] A new class of anticancer compounds has been created that contains both tumour-targeting antibodies and nanoparticles called fullerenes (C60). This delivery system could load several molecules of anticancer drugs such as taxol.[22]

It has been established that nanocarriers get concentrated preferentially in tumours, inflammatory sites, and at antigen sampling sites by virtue of the EPR effect of the vasculature. Once accumulated at the target site, they can act as a local drug depot at the disease site, e.g., solid tumours. Quantom dots, nanotubes, and nanoparticles are being tried as new drug delivery systems. Single-particle quantum dots conjugated to tumor-targeting anti-human epidermal growth factor receptor 2 (HER2) MAb have been used to locate tumours using high-speed confocal microscopy.[23] The nanotubes modified on their outer surfaces with the target antibody showed enhanced attachment to breast-cancer cells. Solid lipid nanoparticles (SLNs) of paclitaxel have been prepared by using glyceryl monostearate, without loss of its anticancer property.[24]

Engineered polymers called "smart polymers" can respond to changes in environmental conditions such as temperature, pH, etc. Drug-polymer conjugates and drug-containing nano/micro-particles have been used for drug targeting and molecular imaging.[25] Indiscriminate drug distribution and severe toxicity of systemic administration of chemotherapeutic agents can be overcome through encapsulation and cancer cell targeting of chemotherapeutics in 400 nm nanocells, which can be packaged with significant concentrations of drugs of different charge, hydrophobicity and solubility.[26] Doses of drugs delivered via nanocells are 1000 times less than the dose of the free drug required for equivalent tumour regression, with superior efficacy. However, nano-sized drug delivery vehicles while being able to achieve high delivery effi-

ciencies, must degrade quickly, and the delivery system itself should be nontoxic to cells.[27]

In conclusion, it must be emphasized that this article does not explore toxicity issues which are only now emerging, but merely highlights the tremendous potential of nanomaterials in medicine. Toxicity issues must be resolved unequivocally before nanomaterials can be routinely employed in medical diagnostics and therapeutics.

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