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Emerging trends of nanoparticle used as novel drug delivery systems and its application

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Abstract

Nanotechnology offers great potential benefits for drug delivery and therapy of respiratory and systemic diseases. Nanoparticles have been of significant interest for some time because they can be designed to simultaneously carry a drug payload, specifically target features of diseased tissues, and carry an imaging molecule to track drug accumulation and clearance in tissues. Moreover, they can be engineered to tailor drug delivery and improve pharmacokinetics. A variety of Nanoparticles have been investigated in experimental animal models as tools to improve the delivery and therapeutic efficacy of drugs or genes delivered to the lung or other organ systems. The nanotechnology platform for drug delivery contains a number of very different types of nanostructures with widely varying properties. Examples of these Nanoparticles include dendrimers, fullerenes, carbon nanotubes, and polymeric Nanoparticles. In contrast to developing completely new drug compounds, introducing upgraded formulations greatly reduces the risk, time and capital invested in new drug development. Nanoparticle drug delivery technology can enable reformulation of existing drugs to increase product lifecycle, increase profitability, expand intellectual property estate and discourage competition during a drug's most valuable years.

Keywords: Nanoparticles, nanotechnology, NDDS.

Introduction

Nanotechnology could be defined as the technology that has allowed for the control, manipulation, study, and manufacture of structures and devices in the "nanometer" size range. These nano-sized objects, e.g.,"nanoparticles", take on novel properties and functions that differ markedly from those seen from items made of identical materials. The small size, customized surface, improved solubility, and multi-functionality of nanoparticles will continue to open many doors and create new biomedical applications. Indeed, the novel properties of nanoparticles offer the ability to interact with complex cellular functions in new ways. This rapidly growing field requires cross-disciplinary research and provides opportunities to design and develop multifunctional devices that can target, diagnose, and treat devastating diseases such as cancer.Nanoparticles for the purpose of drug delivery are defined as submicron (< 1μm) colloidal particles. This definition includes monolithic nanoparticles (nanospheres) in which the drug is adsorbed, dissolved, or dispersed throughout the matrix and nanocapsules in which the drug is confined to an aqueous or oily core surrounded by a shell-like wall . Alternatively, the drug can be covalently attached to the surface or into the matrix. Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural (e.g., gelatin, albumin) or synthetic (e.g., polylactides, polyalkylcyanoacrylates), or solid lipids. In the body, the drug loaded in nanoparticles is usually released from the matrix by diffusion, swelling, erosion, or degradation. A challenge for nanoparticulate drug delivery to the lungs is to understand the fate of particles and their interactions with biological systems. Rapid particle clearance reduces sustained delivery of the drug, and particle translocation might bring nanoparticles to undesired areas of the body. Further exploration into the effect of particle physicochemical properties (e.g. nanoparticle size and material) on extending particle persistence in the lungs and their influence on particle fate is necessary to aid the design of improved systems. The development of inhalable nanoparticle-based delivery systems should draw from the extensive nanoparticle research for injectable applications, including surface modification to target-specific sites.

The toxicology of particulate matter differs from toxicology of substances as the composing chemical(s) may or may not be soluble in biological matrices, thus influencing greatly the potential exposure of various internal organs. This may vary from a rather high local exposure in the lungs and a low or neglectable exposure for other organ systems after inhalation. However, absorbed species may also influence the potential toxicity of the inhaled particles. For nanoparticles the situation is different as their size opens the potential for crossing the various biological barriers within the body. From a positive viewpoint, especially the potential to cross the blood brain barrier may open new ways for drug delivery into the brain. In addition, the nanosize also allows for access into the cell and various cellular compartments including the nucleus. A multitude of substances are currently under investigation for the preparation of nanoparticles for drug delivery, varying from biological substances like albumin, gelatine and phospholipids for liposomes, and more substances of a chemical nature like various polymers and solid metal containing nanoparticles. It is obvious that the potential interaction with tissues and cells, and the potential toxicity, greatly depends on the actual composition of the nanoparticle formulation. This paper provides an overview on some of the currently used systems for drug delivery. Besides the potential beneficial use also attention is drawn to the questions how we should proceed with the safety evaluation of the nanoparticle formulations for drug delivery. For such testing the lessons learned from particle toxicity as applied in inhalation toxicology may be of use. Although for pharmaceutical use the current requirements seem to be adequate to detect most of the adverse effects of nanoparticle formulations, it can not be expected that all aspects of nanoparticle toxicology will be detected. So, probably additional more specific testing would be needed.

Market Impact on Pharmaceutical Industry

The market impact of nanoparticle drug delivery system on pharmaceutical industry will be widely felt, ranging from new specialised treatment for exotic diseases to re-engineering common OTC pain relievers. These new delivery systems will disrupt the generic drug market, since pharmaceutical companies can repackage their brands with expired patents along with newly patented delivery system, so that generics can no longer claim to be brand name equivalents. A recent study of patent activity for nanoparticles in drug delivery shows a clear increasing trend in issued patents (check graph).

Oral delivery of active compounds is expected to remain the primary means of administering drugs for the pharmaceutical industry. A large portion of nano-technology R&D funding will be used in the development of these systems. This will be one of the big success stories in nano-technology-enabled drug delivery. Nano-enabled drug delivery system has high prospects in areas like encapsulation technologies, implantable delivery method, imaging agents and micro-needles.Nanoparticle based delivery system would allow faster drug absorption, controlled dosage release into the human body and would have other unique properties of minimising side-effects by eliminating requirement of co-solvent as used in conventional dosage form. Further, drugs that have side-effects due to triggering an immune system response can be wrapped in nanoparticle coating and prevent immune system from recognising and reacting to a foreign substance.Psividas biosilicon is a nanostructured drug delivery system that allows drug molecules to be held in nanosised particles that release a tiny pulse of drug as the biosilicon dissolves. This is the same material as the microchip that runs a cell phone or computer and has application to a variety of drugs that have problematic delivery and bioavailability characteristics. Biosilicon can be favoured for oral drug delivery system because of its resistance to degradation in acid environment.

Applications and potential benefits

With nanotechnology, a large set of materials with distinct properties (optical, electrical, or magnetic) can be fabricated. Nanotechnologically improved products rely on a change in the physical properties when the feature sizes are shrunk. Nanoparticles for example take advantage of their dramatically increased surface area to volume ratio. Their optical properties, e.g. fluorescence, become a function of the particle diameter. When brought into a bulk material, nanoparticles can strongly influence the mechanical properties, such as the stiffness or elasticity. Example, traditional polymers can be reinforced by nanoparticles resulting in novel materials e.g. as lightweight replacements for metals. Therefore, an increasing societal benefit of such nanoparticles can be expected.

1. Medicine

The biological and medical research communities have exploited the unique properties of nanomaterials for various applications (e.g., contrast agents for cell imaging and therapeutics for treating cancer). Terms such as biomedical nanotechnology, bionanotechnology, and nanomedicine are used to describe this hybrid field.Functionalities can be added to nanomaterials by interfacing them with biological molecules or structures. The size of nanomaterials is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both in vivo and in vitro biomedical research and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug-delivery vehicles.

2. Diagnostics

Nanotechnology-on-a-chip is one more dimension of lab-on-a-chip technology. Biological tests measuring the presence or activity of selected substances become quicker, more sensitive and more flexible when certain nanoscale particles are put to work as tags or labels. Magnetic nanoparticles, bound to a suitable antibody, are used to label specific molecules, structures or microorganisms. Gold nanoparticles, tagged with short segments of DNA can be used for detection of genetic sequence in a sample. Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots, into polymeric microbeads. Nanopore technology for analysis of nucleic acids converts strings of nucleotides directly into electronic signatures.

3. Drug delivery

The overall drug consumption and side-effects can be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach reduces costs and human suffering. An example can be found in dendrimers and nanoporous materials. They could hold small drug molecules transporting them to the desired location. Another vision is based on small electromechanical systems: NEMS are being investigated for the active release of drugs. Some potentially important applications include cancer treatment with iron nanoparticles or gold shells. A targeted or personalized medicine reduces the drug consumption and treatment expenses resulting in an overall societal benefit by reducing the costs to the public health system.

4. Tissue engineering

Nanotechnology can help to reproduce or to repair damaged tissue. This so called “tissue engineering” makes use of artificially stimulated cell proliferation by using suitable nanomaterial-based scaffolds and growth factors. Tissue engineering might replace today’s conventional treatments, e.g. transplantation of organs or artificial implants. On the other hand, tissue engineering is closely related to the ethical debate on human stem cells and its ethical implications.

5. Chemistry and environment

Chemical catalysis and filtration techniques are two prominent examples where nanotechnology already plays a role. The synthesis provides novel materials with tailored features and chemical properties e.g. nanoparticles with a distinct chemical surrounding (ligands) or specific optical properties. In this sense, chemistry is indeed a basic nanoscience. In a short-term perspective, chemistry will provide novel “nanomaterials” and in the long run, superior processes such as “self-assembly” will enable energy and time preserving strategies. In a sense, all chemical synthesis can be understood in terms of nanotechnology, because of its ability to manufacture certain molecules. Thus, chemistry forms a base for nanotechnology providing tailor-made molecules, polymers etc. and furthermore clusters and nanoparticles.

6. Filtration

A strong influence of nanochemistry on waste-water treatment, air purification and energy storage devices is to be expected. Mechanical or chemical methods can be used for effective filtration techniques. One class of filtration techniques is based on the use of membranes with suitable hole sizes, whereby the liquid is pressed through the membrane. Nanoporous membranes are suitable for a mechanical filtration with extremely small pores smaller than 10 nm ("nanofiltration"). Nanofiltration is mainly used for the removal of ions or the separation of different fluids. On a larger scale, the membrane filtration technique is named ultrafiltration, which works down to between 10 and 100 nm. One important field of application for ultrafiltration is medical purposes as can be found in renal dialysis. Magnetic nanoparticles offer an effective and reliable method to remove heavy metal contaminants from waste water by making use of magnetic separation techniques. Using nanoscale particles increases the efficiency to absorb the contaminants and is comparatively inexpensive compared to traditional precipitation and filtration methods.

7. Energy

The most advanced nanotechnology projects related to energy are: storage, conversion, manufacturing improvements by reducing materials and process rates, energy saving e.g. by better thermal insulation, and enhanced renewable energy sources.

8. Reduction of energy consumption

A reduction of energy consumption can be reached by better insulation systems, by the use of more efficient lighting or combustion systems, and by use of lighter and stronger materials in the transportation sector. Currently used light bulbs only convert approximately 5% of the electrical energy into light. Nanotechnological approaches like light-emitting diodes (LEDs) or quantum caged atoms (QCAs) could lead to a strong reduction of energy consumption for illumination.

9. Recycling of batteries

Because of the relatively low energy density of batteries the operating time is limited and a replacement or recharging is needed. The huge number of spent batteries and accumulators represent a disposal problem. The use of batteries with higher energy content or the use of rechargeable batteries or supercapacitors with higher rate of recharging using nanomaterials could be helpful for the battery disposal problem.

10. Information and communication

Current high-technology production processes are based on traditional top down strategies, where nanotechnology has already been introduced silently. The critical length scale of integrated circuits is already at the nanoscale (50 nm and below) regarding the gate length of transistors in CPUs or DRAM devices.

11. Novel semiconductor devices

An example of such novel devices is based on spintronics. The dependence of the resistance of a material (due to the spin of the electrons) on an external field is called magnetoresistance. This effect can be significantly amplified (GMR - Giant Magneto-Resistance) for nanosized objects, for example when two ferromagnetic layers are separated by a nonmagnetic layer, which is several nanometers thick (e.g. Co-Cu-Co).

The GMR effect has led to a strong increase in the data storage density of hard disks and made the gigabyte range possible. The so called tunneling magnetoresistance (TMR) is very similar to GMR and based on the spin dependent tunneling of electrons through adjacent ferromagnetic layers.Both GMR and TMR effects can be used to create a non-volatile main memory for computers, such as the so called magnetic random access memory or MRAM.

12. Novel optoelectronic devices
In the modern communication technology traditional analog electrical devices are increasingly replaced by optical or optoelectronic devices due to their enormous bandwidth and capacity, respectively. Two promising examples are photonic crystals and quantum dots .

Photonic crystals are materials with a periodic variation in the refractive index with a lattice constant that is half the wavelength of the light used. They offer a selectable band gap for the propagation of a certain wavelength, thus they resemble a semiconductor, but for light or photons instead of electrons.

Quantum dots are nanoscaled objects, which can be used, among many other things, for the construction of lasers. The advantage of a quantum dot laser over the traditional semiconductor laser is that their emitted wavelength depends on the diameter of the dot. Quantum dot lasers are cheaper and offer a higher beam quality than conventional laser diodes.

13. Displays
The production of displays with low energy consumption could be accomplished using carbon nanotubes (CNT). Carbon nanotubes can be electrically conductive and due to their small diameter of several nanometers, they can be used as field emitters with extremely high efficiency for field emission displays (FED). The principle of operation resembles that of the cathode ray tube, but on a much smaller length scale.

Advantages of nanoparticle drug delivery
For biotherapeutics such as insulin, delivery to the lungs is a non-invasive method for systemic exposure over intravenous injection. Nanoparticles could provide the advantage of sustained release in the lung tissue and thus the systemic circulation, resulting in a reduction in dosage frequency and improved patient compliance. Insulin is an important example for which the delivery of the drug to the lungs has been shown to be beneficial. A study by Kawashima *et al.* dosed PLGA nanoparticles prepared with insulin to guinea pig lungs and demonstrated a significant reduction in blood glucose level, with a prolonged effect over 48 h as compared to insulin solution. Additionally, insulin-loaded nanoparticles using a different polymer, poly(butyl cyanoacrylate), delivered to the lungs of rats were shown by Zhang *et al.* to extend the duration of a hypoglycemic effect over 20 h (glucose level below 80% of the original levels) as compared to pulmonary administration of insulin solution.

Strategies to modify nanoparticles
Prolonging drug presence can be manipulated by using mucoadhesive materials, such as the biodegradable polysaccharide chitosan. Yamamoto *et al.* produced PLGA nanoparticles surface-modified with chitosan and encapsulating the peptide elcatonin. Nanoparticles delivered to the lungs of guinea pigs produced significant reductions in blood calcium levels relative to the initial calcium concentrations, with prolonged effects up to 24 h. This was significantly longer than results obtained with unmodified nanoparticles. The chitosan-modified nanoparticles were shown

to be eliminated more slowly than the unmodified version, which suggests that sustained effects were a result of retention of nanoparticles.

Targeting nanoparticles for local lung delivery

The pulmonary delivery of nanoparticles also has the potential to increase and sustain local lung drug concentration for the treatment of respiratory diseases. Targeting the site of action could decrease the required body dose, thus reducing systemic side effects. Moreover, oral dosing variability resulting from changing gastric conditions could be avoided. Vaughn *et al.* explored local delivery of itraconazole (ITZ) nanoparticles to treat *Aspergillus fumigatus* fungal infections, which typically enter the body through the lungs and disseminate through the lymph system. Treatment requires a balance of high and sustained lung concentrations while maintaining serum levels above the minimum lethal concentration (MLC) to *A. fumigatus*, yet at a lower maximum serum concentration (as compared to oral) to reduce toxicity.

Technical issues of nanoparticle applications

Nanoparticles are most often delivered to the lungs by nebulization of colloidal solutions. However, nanoparticles stored in an aqueous medium will, over time, lead to polymer hydrolysis and loss of drug. Solution instability is another concern owing to particle agglomeration and settling, a result of the small size and strong particle–particle interactions of nanoparticles, which could lead to poor functionality of the nebulizer. To prepare nanoparticles for ultimate commercial use, lyophilization of nanoparticles has been explored as a means to provide a storage form that can be rehydrated to deliver nanoparticles in solution and . Resuspension is difficult and the retention, post-hydration, of the same nanoparticle size requires the use of large amounts of stabilizers during the freeze-drying process. These cryoprotectant sugars and surfactants remain in the reconstituted solution and are delivered along with the particles. Moreover, individual nanoparticles do not deposit efficiently in the lungs by diffusion, sedimentation or impaction, which results in the exhalation of a majority of the inhaled dose.

Conclusion

Nanoparticles are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. A bulk material should have constant physical properties regardless of its size, but at the nano-scale this is often not the case where size-dependent properties are often observed. Thus, the properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant. For bulk materials larger than one micrometer (or micron), the percentage of atoms at the surface is insignificant in relation to the number of atoms in the bulk of the material. The interesting and sometimes unexpected properties of nanoparticles are therefore largely due to the large surface area of the material, which dominates the contributions made by the small bulk of the material. Scientists have taken to naming their particles after the real world shapes that they might represent. Nanospheres nanoreefs, nanoboxes and more have appeared in the literature. These morphologies sometimes arise spontaneously as an effect of a templating or directing agent present in the synthesis such as miscellar emulsions or anodized alumina pores, or from the innate crystallographic growth patterns of the materials themselves. Some of these morphologies may serve a purpose, such as long carbon nanotubes being used to bridge an electrical junction, or just a scientific curiosity like the stars shown at right. Nanoclusters have at least one dimension between 1 and 10 nanometers and a narrow size distribution. Nanopowders are agglomerates of ultra fine particles, nanoparticles, or nanoclusters. Nanometer-sized single crystals, or single-domain ultrafine particles, are often referred to as nanocrystals. Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications in biomedical, optical and electronic fields.

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