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New modalities for drug delivery in the treatment of chronic diseases through Nanosize drug delivery systems

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Abstract

Nanotechnology has a revolutionary impact on medical diagnosis and therapy. Targeted therapy and localized drug delivery have been the key challenges in the treatment of life threatening diseases. Nanotechnology has far-reaching implications that hold the promise of providing great leaps in the area of medical treatment in terms of detecting, diagnosing and treating complicated medical conditions. Nanotechnology helps in early detection, appropriate treatment and also to detect undesired effects of the drug that can correct the problem well before managing of the disease completely goes out of hand. Research and diagnosis will become far more efficient through the application of nanotechnology, allowing rapid response to new diseases, allowing continuous health monitoring resulting in several new kinds of treatment which makes the practice of medicine cheaper, more precise and available to more people at affordable costs. The following review attempts to provide a better understanding of the current and future applications of nanotechnology in various fields of medicine focused on drug delivery systems.

Key words: Nanotechnology, Drug Delivery, Nanomedicine, Challenges, Future Prospects

Introduction

The primary focus of Nanosize drug delivery systems is formulating bioactive molecules in biocompatible nanosystems such as

- nanocrystals,
- solid lipid nanoparticles,
- nanostructure lipid carriers,
- lipid drug conjugates,
- nanoliposomes,
- dendrimers,
- nanoshells,
- emulsions,
- nanotubes,
- quantum dots etc.

Approaches in the field of Nanotechnology and Drug Delivery

The different approaches in the field of Nanotechnology and Drug Delivery are

1. Nanosuspensions And Nanocrystals
2. Solid Lipid Nanoparticles
3. Nanotubes And Nanowires
4. Polymeric Nanoparticles
5. Pegylated-Liposomes
6. Conventional Liposomes
7. Immunoliposomes
8. Niosomes
9. PLGA NPs
10. PHDCA or HDCA NPs
11. Chitosan Nanospheres Conjugated With PEG
12. Stealth and Non Stealth SLN
13. PBCA-SLNs
14. Albumin NPs

1. Nanosuspensions and Nanocrystals

Drug compounds are best used for the nanosuspension technology, if they form crystals with high energy content, which renders them insoluble in either organic (lipophilic) or hydrophilic media.Nanosuspensions can be used for increasing bioavailability after oral application, e.g. amphotericin B, danazol or tacrolimus. In addition, several solubility related problems of poorly soluble drugs can be resolved, such as a reduced variability of absorption, a faster onset of action, and improved dose proportionality (Van Eerdenbrugh et al., 2008).

2. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles as a colloidal carrier system for controlled drug delivery.

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Main reason for their development is the combination of advantages from different carriers systems like liposomes and polymeric nanoparticles (Mukherjee et al.,2009).

Cationic solid lipid nanoparticles (SLN) for gene transfer can be formulated using the cationic lipids as for liposomal transfection agents.

Stealth and non stealth SLNs

These stealth liposomes are spherical vesicles with a membrane composed of phospholipids bilayer used to deliver drugs or genetic material into the systemic circulation(Fundaroet al., 2000). Solid lipid nanoparticles (SLNs) can be efficiently used as colloidal drug delivery systems for incorporating hydrophilic or lipophilic drugs and various macromolecules as well as proteins and nucleic acids and they offer great promise for controlled and site specific drug and gene delivery (EzzatiNazhad et al., 2015).

Nanotubes and Nanowires

Nanotubes are considered as spherical self assembling lipid molecules.

Advantage of these spherical nanoparticles is

1. the increased internal volume, and
2. the option to functionalize the inner or external surface.

From its dimension nanotubes show a diameter up to 100 nm and a length from several up to hundreds of microns. The cylindrical geometry allows encapsulation of the drug followed by the fabrication and modification of the vehicle.Drugs can be covalently bound on the surface but mostly remain diffusion controlled in the internal volume (Lacerda et al.,2006).

Polymeric nanoparticles

Biodegradable polymers and their co-polymers are used to prepare polymeric nanoparticles.These polymeric nano-carriers include micelles, capsules, platelets, fibers, spheroids colloids, dendrimers, core-shells, nanoparticle incorporated polymer matrixes, etc.Generally the drug loaded nanoparticles were prepared by dissolving the drug and polymer into the water-immiscible organic solvents (Chan et al.,2010).

Polymeric nanoparticles (PNPs) consists of a biodegradable polymer. The advantages of using PNPsin drug delivery are many, being the most important that they generally increase the stability of any volatile pharmaceutical agents and that they are easily and cheaply fabricated in large quantities by a multitude of methods. Also, polymeric nanoparticles may have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location.

Polymeric nanoparticles can be easily incorporated into other activities related to drug delivery, such as tissue engineering and represent a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.

Drawbacks in polymerization techniques are evolving noxious factors such as toxic, reactive residues, un-reacted monomers, the risk of a chemical reaction and the formation of unwanted oligomers.

3. **Pegylated-liposomes**

PEGylation, in which countless moleculesof a synthetic, nontoxic polymer, polyethylene glycol (PEG), are attached, at one end of the polymer chain, to the surface of the liposome (Milla et al.,2012).It is a powerful and flexible strategy to improve the drug delivery. PEGylation is one of the most successful strategies to improve the delivery of therapeutic molecules such as proteins, macromolecular carriers, small drugs, oligonucleotides, and other biomolecules.

4. **Conventional liposomes**

These are liposomes that are typically composed of only phospholipids.They can vary widely in their physicochemical properties such as size, lipid composition, surface charge and number and fluidity of the phospholipid bilayers. Manipulation of these properties is a valuable tool to modify, the in vivo behavior of conventional liposomes (i.e. stability, clearance and distribution)(Abolfazl et al.,2013), however, some of the in vivo behavioral features are very consistent among different conventional-liposome formulations. Conventional liposomes are characterized by a relatively short blood circulation time.

5. **Immunoliposomes**

Immunoliposomes are generated by coupling of antibodies to the liposomal surface. They allow for an active tissue targeting through binding to tumor cell-specific receptors (Paszko and Senge, 2012). They are of great interest for their potential use in specific drug delivery to cancer cells, gene therapy, drug delivery through blood brain barrier, or molecular imaging.

6. **Niosomes**

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes (Buckton&Harwood,1995).Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer.

7. **PLGA NPs**

Hydrophobic and hydrophilic drugs are encapsulated in Poly(lactic-co-glycolic acid) (PLGA) particles via single- or double-emulsion. Briefly, the drug is

dissolved with polymer or emulsified with polymer in an organic phase that is then emulsified with the aqueous phase. After the solvent has evaporated, particles are washed and collected via centrifugation for lyophilization and long term storage (Fabienne et al., 2012). Advantage being, PLGA degrades slowly via hydrolysis in aqueous environments, and encapsulated agents are released over a period of weeks to months.

Although PLGA is a material that possesses many advantages for drug delivery, reproducible formation of nanoparticles using PLGA can be challenging; considerable variability is introduced by the use of different equipment, reagents batch, and precise method of emulsification.

Chitosan nanospheres

Chitosan is a promising biopolymer for drug delivery systems and has wide applications in both drug delivery and wound healing (Felt et al., 1998).Chitosan is considered the most important polysaccharide for various drug delivery purposes because of its cationic character and primary amino groups, which are responsible for its many properties such as

- mucoadhesion,
- controlled drug release,
- transfection, in situ gelation,
- efflux pump inhibitory properties and
- permeation enhancement

PBCA-SLNs

Nanoparticles of poly(butylcyanoacrylate) (PBCA) were reported to achieve successful delivery of drugs (small as well as large) to the brain by crossing the blood-brain barrier (BBB). Limitation being lack of stability of the interaction between the absorbed drug and the nanoparticle(TorstenandRainer, 2005).

Albumin NPs

Albumin is an attractive nanoparticle carrier widely used to prepare microspheres and microcapsules due to its easy bioavailability, antitoxicity, non immunogenecity, it's easy biodegradation, lack of antigenicity, improved patient compliance (Kratz, 2008).

Albumin accumulates in solid tumors making it a potential macromolecular carrier for site directed delivery of antitumor drugs (Takakura et al., 1990).

Next generation of drug delivery systems

Biomimetic polymers and biomimetic methods seems to be realistic in constructing nanoelectronic devices that could detect the concentrations of biomolecules in real time for use as medical diagnostics (Hilt, 2004).Nanoelectronic devices which could interact with single cells for use in basic biological research are called nanosensors that should enable new approaches for health monitoring, surveillance, and defense technology.

Microelectronics - Electronic devices have been miniaturised and reached a stage of dimension being close biological macromolecules.Molecular electronics use the same self-assembling processes as biomolecules, combining both technologies will lead to the design of ultrafast, ultra small and biocompatible device which scaled-down machining and computing.

• Nanoparticles are widely used for diagnostic, screening and drug delivery purposes, DNA sequencing, and viral detection.

• Nanotechnology (derived from the Greek word *nano*, meaning dwarf) is a rapidly growing multidisciplinary scientific field that applies engineering and manufacturing principles at a molecular level.

Applications and research targets of nanomedicine

Nanoparticles have been designed with chemically modifiable surfaces onto which various ligands attach, which can turn these Nanomaterials into biosensors, molecular-scale fluorescent tags, imaging agents, targeted molecular delivery vehicles, and others.

Challenges with Nanoparticles

Nanoparticles can become toxic because they take on catalytic properties and become biologically engulfable.

Managing Toxicity of Nanomaterials

Serious issues related to patient safety and possible secondary effects related to the use of nanoparticles.

Nanoparticles can have a natural or biological origin—like viruses— or be engineered, including very different elements. It is their small size that gives nanoparticles their unique electrical, optical, and chemical properties, raising concerns about their potential toxicity (Amela et al., 2010).

More research on the physico-chemical properties of nanomaterials, such as size, shape, crystalline structure, chemical composition, and how all these present, whether in vivo or invitro, are necessary.

In this regard, controversies have arisen when research articles suggest that nanoparticles can damage DNA or specific cells. In some cases, studies in vitro may have little relevance to human exposure risks or may be even deeply flawed. In some cases, it is the dose and mechanism of action that makes a nanoparticle therapy toxic, rather than the properties of the nanoparticle itself.

Future Prospects

- ✓ Thousands of measurements can be done very rapidly and very inexpensively.
- ✓ Biochip technology to the nanoscale range.
- ✓ Molecular electronics and nanoscale chemical sensors

- ✓ Will enable the construction of microscopic sensors capable of detecting patterns of chemicals in a fluid.
- ✓ Will facilitate the development of non-PCR diagnostic technologies.
- ✓ Used for analysis of a single cell for preimplantation genetic diagnosis.
- ✓ the use of nanodiagnostics could reduce waiting time for test results, thus decreasing patient anxiety, improving compliance, and making the whole process less costly
- ✓ In the next decade nanobiotechnology will play important roles not only in diagnosis but also in linking diagnosis with treatment and development of personalized medicine.
- ✓ Molecular diagnosis of cancer, including genetic profiling,
- ✓ Nanorobotics may be applied in the future for early detection as well as treatment of cancer.
- ✓ Preventive personalized management of cancer
- ✓ A nanodevice for combined diagnosis and therapeutics could be implanted as a prophylactic measure in individuals who do not exhibit any obvious manifestations of cancer, and cancer surveillance could be conducted by external remote monitoring.
- ✓ Early detection of diseases would increase the chances of cure.

Conclusion

All the applications may all seem highly unlikely, implausible, or even heretic and also exciting and exaggerating.Though at present these concepts appear theoretical, can become applicable and in turn a reality more rapidly.

As with all technologies, nanotechnology carries a significant potential for misuse and abuse on a scale and scope never seen before.However, nanotechnology, has the potential to bring about significant benefits, such as improved health, better use of natural resources, and reduced environmental pollution.Nanoparticles have been designed with chemically modifiable surfaces onto. Toxicological problems have to be faced and solved in the future. The problems will arise, if poorly soluble particles and non-biodegradable particles are used for long term or life time therapy like diabetes, asthma or rheumatoids.

Nanotechnologies promise to extend the limits of current molecular diagnostics and enable point of- care diagnosis, integration of diagnostics with therapeutics, and development of personalized medicine.

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