Nanotechnology Based Drug Delivery at Cellular Level: a Review

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Abstract

Nanotechnology based drug delivery systems have potential to revolutionize theranostics. Efficient drug delivery and the favorable fate thereafter can be achieved by proper understanding of the interactions of nanomaterial with the biological environment, mechanisms of uptake, intravascular and intracellular trafficking, biological distribution, site specific delivery, controlled drug release and therapeutic action. Nano drug delivery systems have overcome the problems of drug resistance in target cells and have facilitated movement of drugs across barriers for efficient targeting of affected cells and the molecules involved in disease process. Most of these cellular and molecular mechanisms are poorly understood. Besides, despite being scanty the issues related to metabolism and toxicity of nanoparticles after therapeutic action, need to be addressed so as to enable safe and effective treatment of diseases.

Keywords: Nanoparticles, drug delivery, cellular.
NANOTECHNOLOGY BASED DRUG …

Introduction

Since the inception of concept of nanoscience in 1959 by Richard Feynman who discussed the promise of miniaturization of materials down to the nanoscale (Feynman, 1959) there has been tremendous progress in this field. Nanotechnology originally used by Nario Taniguchi in 1974 (Taniguchi, 1974) for the composite word to signify machining with tolerances of less than one micron, has found great potential in drug delivery now a days. Novel nano drug delivery systems are being designed for efficient and safe drug disposition in the affected tissues (Jong and Borm, 2008). Efficient drug delivery and the favorable fate thereafter can be achieved by proper understanding of the interactions of nanomaterial with the biological environment, mechanisms of uptake, intravascular and intracellular trafficking, biodistribution, receptor binding and site specific delivery, time dependent controlled drug release and therapeutic action (Sandhiya et al., 2009, Suri et al., 2007). Though nano drug delivery systems have overcome the problems of drug resistance in target cells and have facilitated movement of drugs across barriers for efficient targeting of affected cells and the molecules but the mechanisms underlying these are yet to be explored (Ying Zhang et al., 2013). Besides metabolism and toxicity issues in some nanoparticles need to be addressed for better therapeutic reputation.

Importance of Nanoparticles

Nanoparticles used as drug delivery vehicles are generally < 100 nm in at least one dimension, and consist of different biodegradable materials such as natural or synthetic polymers, lipids, or metals (Suri et al., 2007, Abhilash, 2010). They consist of different biodegradable materials such as natural or synthetic polymers, lipids, or metals (Eidi et al., 2012). Nanoparticles are taken by cells more efficiently than larger micromolecules and therefore could be used as effective transport and delivery system. Nanodevices are innovative and can provide a wide range of advantages (Tocco et al., 2012): from the ability of nanoparticles to enter into the cytoplasmic space across cellular barriers and activate specific transport mechanisms (Sandhiya et al., 2009, Suri et al., 2007); to the modulation of drugs biocompatibility, bioavailability and safety profiles through nano delivery systems (Medintz et al., 2008). Effective targeting through nanoparticles can be done by attaching ligand (Yu et al., 2012, Debjit Bhowmik et al., 2009). Drugs for specific delivery may be integrated either in matrix or surface. Solubility of insoluble drugs is increased (Tiwle et al., 2012; Fairhurst et al., 2012). Application of nanoparticles enables to overcome-resistance (Fairhurst et al., 2012). Use of nanoparticles minimizes toxicity. Besides nanoparticles facilitate controlled release of drug (Farokhzad et al., 2009).

Drug Delivery in Nanotechnology

Nanoparticles used for drug delivery in nanotechnology may be lipid-based nanoparticles (liposomes), polymer-based nanoparticles (dendrimers, fullerenes), metal-based nanoparticles (quantum dots, nano shells) or biological nanoparticles. Liposomes are most studied nanoparticles used for drug delivery. They are bilayered vesicles with aqueous volume enclosed by membranous lipid bilayer e.g. Doxil (Zhao et al., 2013). A dendrimer is technically a synthetic polymer; three-dimensional macromolecules formed using a nanoscale fabrication process. It has tree-like structure e.g. Polyamidoamine i.e. PAMAM (Tian et al., 2013). Fullerenes (Bucky balls) are composed of at least 60 atoms of carbon each bonded to 3 other atoms. They are perfectly smooth, round and hollow inside, inert and nontoxic. They are used in therapeutic and diagnostic imaging (Kroto et al., 1985). Nanotubes are a sequence of nanoscale C60 atoms arranged in a long thin cylindrical structure. Buckyballs when expanded from the center into cylinder become nanotubes. Nanotubes are also called buckytubes (Elhissi et al., 2012). Quantum dots are crystalline structure, from inorganic substances and have Core (CdSe), shell (ZnS) and Cap (SiO2). Absorbs white light and then reemits it later in a specific color which depends on the size of QD. Carry siRNA to cells, used as molecular labels for tumor targeting (Degim et al., 2013). Nanoshells are concentric spherical glass particles with an outer shell of gold and silica core. They are useful in destroying tumor cells (Bardan et
The most recent moieties are exosomes (Zhuang et al., 2013).

**Methods of Drug Delivery**

There are different methods by which a nanoparticle can be administered (Vauthier, 2011). It can be injectable (Doxil), oral (Insulin-Polyethylcyanoacrylate nanospheres), intradermal (local anesthetics), implantation (hormones) or inhalations (nanocrystals).

**Therapeutic Delivery**

After the nanoparticle has been administered it reaches blood circulation and the half life of the drug it carries gets prolonged as it is retained for quite some time. When the nanoparticle reaches diseased blood vessel (inflamed or neoplastic vessel) time dependent extravasation occurs passively or active targeting may facilitate nanoparticle binding to affected vessels. In case of inflammation or tumour there is enhanced permeability retention (EPR) effect (Matsumura et al., 1986), which depends on biophysicochemical properties of nanoparticles. Nanoparticle uptake has been reviewed recently by Lesniak et al., (Lesniak et al., 2013). After the nanoparticle have accumulated in affected tissue there may be:

- Ligand mediated targeting in vascular endothelium targeting. This is applied in oncology and cardiovascular indications.

- Active targeting and receptor mediated endocytosis involving the receptors expressed in affected tissue. There will be intracellular accumulation.

- Size mediated targeting e.g. in immunological tissue. Based on the above mechanisms there will be increased therapeutic efficacy, especially of drugs which do not pass membrane and drugs which require intracellular receptor for action (Hillaireau et al., 2009).

Inside blood circulation nanoparticles are not recognised by immune system. They are not screened out of circulation by liver and spleen. This may be due to their small size which is usually less than 200nm (www.nanopharmaceuticals.org.) and/or inert coatings like PEGylation (Freitas, 2005). One of the examples for this is stealth liposomes which are coated by PEG and carry doxorubicin (Immordino et al., 2006).

**Targeting**

Targeting may be passive targeting or active targeting. In case of passive targeting simple extravasation may occur which depends on biophysicochemical properties. This is applicable to non-surface modified nanoparticles.

Efficacy of nanoparticles as delivery vehicles is highly size and shape dependent. The size of the nanoparticles affects their movement in and out of the vasculature, whereas the margination of particles to vessel wall is impacted by their shape (Farokhzad et al., 2012). Active targeting involves using a multicomponent nanoparticle containing therapeutic as well as biological surface modifying agents (Decuzzi et al., 2008) enables site specific delivery. Active targeting ligands may be small molecules (e.g. galactose, manose, folate, and pectin), peptides (e.g. RGD) or proteins (e.g. transferring, antibodies, LDLs).

Targeting lectins: Antileishmanial drugs targeting through glycosylated polymers specifically internalized by macrophage membrane lectins are being used (Negre et al., 1992).

Targeting Cellular folate receptors: In this case a dendrimer docks on cellular folate receptors, which are over-expressed on the surface of cancer cells. In addition the dendrimer contains an indicator called fluorescein and an anticancer drug such as methotrexate. The dendrimer delivers the drug to malignant cells and marks them with fluorescein as well (Farokhzad et al., 2009).

Targetting peptides: In case of tumours, angiogenesis mediators or receptors (Integrin αvβ3 and vascular endothelial growth factor (VEGF) receptor) are targeted. Synthetic peptide Arg-Gly-Asp (RGD) is specific to integrin αvβ3 and inhibits tumour growth and proliferation. This is employed in glycol chitosan coated nanotubes. Similarly ICAM-1 which is upregulated in inflammation and several cancers is targeted using RGD derived peptides.

HER2 receptor in human breast cell cancer is targeted using monoclonal antibody (Couzin et al., 2002). Nab-platform (nanoparticle albumin bound) utilizes endogenous albumin pathways of
endothelial transcytosis (gp60) and intratumoral binding of SPARC (secreted protein acidic and rich in cysteine).

**Drug Release Approaches**

Passive i.e. the release of the drug can’t be controlled but happens over time or have not been worked well (Järvinen et al., 2007). Accumulated nanoparticles with drug inside can be melt by near infra red light (NCI), laser light (complicated), low frequency radio waves which has no ill effects (Stanley et al., 2012) or low frequency focused ultrasound e.g. Doxceril-liposome (Schroedera et al., 2012).

Glutathion (GSH) sensitive linkers enable fast drug release from dendrimer conjugates at intracellular glutathion level but not in blood circulation (Navath et al., 2008). Enzyme triggered release e.g. secretory phospholipase2 (SPLA2) enables drug release from nanoparticles (Andresen et al., 2005). Temperature triggered release is applicable for lysophospholipids and pH triggered release for oleic acid and cholesteryl hemisuccinate (CHEM) based liposomes.

**Metabolism**

The nonspecific adsorption of serum proteins may dictate the cellular fate, uptake, metabolism and clearance of nanoparticles (Przybytkowski et al., 2009). Lipid based drug delivery systems (parenteral emulsion and Solid lipid nanoparticles-NPs) are metabolized by endogenous enzymes like alcohol dehydrogenase (Dong, 2009).

**Toxicity Issues**

Toxicity issues of nanoparticles have been reviewed (Yah et al., 2012, Love et al., 2012). Toxic issues are more serious for intravenously injected nanoparticles which cause oxidative stress and apoptosis e.g., carbon nanotubes. Besides cadmium used in some nanoparticles is toxic e.g., Cadmium selenide QDs. Poly cationic lipids cause cell death via apoptosis or necrosis or both. Cytotoxic to immune cells is also reported e.g., Poly (L-lactic acid). Further nanoparticles can be mutagenic.

**Conclusion**

Nanotechnology has revolutionized drug delivery systems. Nanoparticles based drug delivery has overcome the barriers to pass no reachable sites and has enabled efficient targeting of cells and molecules. Besides it has minimized drug resistance and has improved the efficiency of drugs through efficient and site specific delivery. Still better understanding of cellular and molecular moieties involved in disease process and their interaction with nanoparticles will enable development of future drugs that will be more site specific, safe and effective.

**References**


Tiwle R, Ajazuddin Giri TK, Tripathi DK, Jain V and Alexander A (2012). An Exhaustive review on solubility enhancement for hydrophobic compounds by possible


