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Toxicity in Cadmium Containing Quantum Dots

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Abstract: Quantum dots are nanoscale semiconductors made from materials such as cadmium selenide, cadmium sulphide, indium arsenide or zinc sulphide and are extensively used in electronics, optoelectronics and biomedical sciences. Manipulation of these Quantum Dots is opening a world of creative possibilities and the benefits are expected to have substantial impact on almost all industries and areas of society such as medicine, plastic, energy, electronics and aerospace etc. Although Quantum Dots offer potentiality invaluable societal benefits such as drug targeting and biomedical imaging but at the same time these may also pose risks to human health and environment under certain conditions as reviewed literature suggests. In this paper we have reviewed and discussed the potential toxicity of cadmium containing Quantum Dots which depends upon multiple physicochemical as well as on environmental factors.

Keywords: Quantum Dots (Q Dots), toxicity, nanomaterials, cytotoxicity

Introduction

Q Dots are nanoscale semiconducting material with diameter ranging from 2 to 10 nanometers, having unique and a valuable property of fluorescent material, which renders them optimal fluorophores for bio-imaging. Q Dots consist of two free functional groups for binding with drug molecule. The outer shell of Q Dot is made of semiconducting material which provides the surface for bio-conjunction leading to improvement in aqueous solubility. Surface modification of Q Dots through covalent and noncovalent binding, affects and alters the property of drug molecule. Their cellular delivery is mediated by passive transport, facilitative delivery and active transport. The shell structure of Q Dot reduces the toxicity of core material which is generally made of heavy material like cadmium (Cd).

Table 1: Analysis of Cadmium Containing Q Dots

Physicochemical properties	Toxicity assessment	Toxicity mechanisms	Potential routes of exposure
Particle size	*In vitro* toxicity	Cd^{2+} release	Environmental media
Shape	Viability	ROS generation	Workplace
Core composition	Oxidative stress	Nano-size effects	Diagnostic administration
Charges	Genotoxicity	Autophagy	
Surface coating	Apoptosis		
Stability	*In vivo* toxicity		
	Body weight		
	Histological analysis		
	Bioaccumulation		
	Biodistribution		

The Q Dots toxicity depends on several factors derived from both individual Q Dot physicochemical properties and environment conditions such as outer coating material (capping material i.e., functional group), size, charge, concentration, oxidative, photolytic

and mechanical stability etc. (Hsieh 1991, Green 2010). Some Q Dots have been found to be cytotoxic after oxidation or photolytic degradation of their core coatings. The Toxicity of Q Dots have been also studied from the exposure routes of the regarding material of similar size and physicochemical properties. It is observed that the potential routes of Q Dots exposure are environmental media, workplace and therapeutic or diagnostic administration (Green 2010).

Exposure through environment is a potential route because of Q Dot metalloid core compositions and that of Q Dot core coating. Few Q Dot core metals like Cd, Se are observed to be toxic to vertebrates at low concentrations part per million (ppm). The toxicity depends upon many factors e.g., dose, concentration, duration, frequency of exposure, mechanical stability, photolytic degradation, half-lives and partitioning into the environment etc., However it is yet to be established that how these Q Dot partition into environment media and that what is the stability of Q Dots in the environment product lifetimes? But there is always a risk of leakage and spilling of Q Dot materials during their manufacturing and transport disposal and these are the potential sources of toxicity in environment as well.

Following reasons can be attributed to the Q Dots' environmental exposure (EE):

- EE depends upon on the place e.g., air, water, soil where the Q Dots materials partition
- The length of the half-lives of the materials which may run from months to years
- As the Q Dots have very wide applications and hence their production volume is also high which further leads to EE in the similar proportion of their use

Inhalation, dermal contact or ingestion are other ways of exposure for the working professionals at their respective workplaces. Depending on coating thickness, Q Dots vary in size from 2.5 to 100 nm and vary in their sites of deposition in pulmonary tissues once aerosolized. Q Dots less them 2.5 nm may reach the deep lungs and interact with the alveolar epithelium, while larger them 2.5 nm aerosolized Q dots deposit in bronchial spaces. Inhalation exposure may pose potential risks as it may reside in cells for weeks to months. The risks exposure via dermal absorption and accidental ingestion is currently not known.

Cadmium Containing Quantum Dots

There are many types of Q Dots that are prepared and synthesized by the researchers. Among these Q Dots cadmium containing Q Dots are one of the most widely used due to their easy synthesis, high luminous efficiency, excellent monochromaticity and these cover complete visible region of the spectrum (Liang Hu 2021, Wang Y. B 2014). The Cd containing Q Dots have many advantages regarding detection, sensitively in biological applications. However, cadmium is considered as a toxic heavy metal, hence the toxicity of Cd containing Q Dots is a pioneer topic in the field of nanotoxicology. It has been observed that Q Dots corroded, oxidized and also dissolved by the microenvironment after entering organism, which may produce toxicity. Table 1 shows the properties and toxicity of Cd-containing Q Dots.

The core of different Q Dots contains heavy metal elements, due to which significant toxicity gets produced once released outside. Hence in order to increase stability and promote the biosafety of the Q Dot, a stable shell structure is made outside the Q Dot, as per different needs to increase the water solvability or bio-melting of the Q Dot (Liang Hu 2021).

Use of naked Q Dots is more harmful as compared to the Q Dots with phosphatidyl ethanolamine glycol) (PEG) coating or that with ZnS shell. The coating and shell on Q

Dots have proved to be effective measures beneficial to cell proliferation. Comparative studies have been done about cytotoxicity of three kinds of Cd containing Q Dots e.g., CdTe, CdTe / CdS and CdTe/ CdS /ZnS (Su y. 2009).

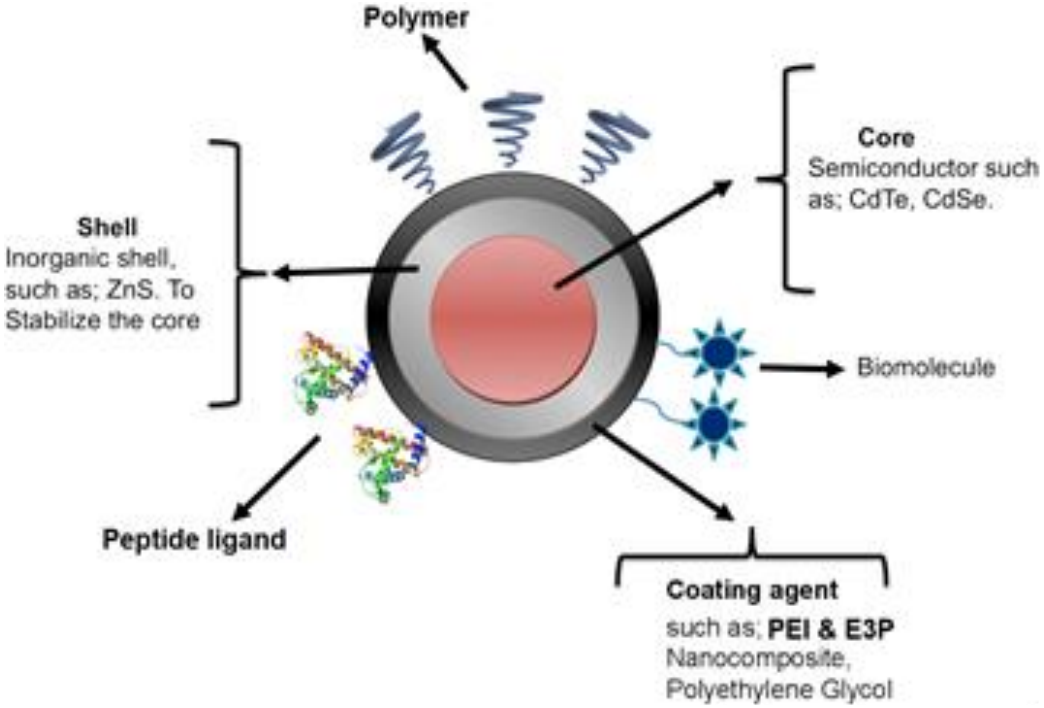

Fig. 1: Structure of quantum dot with bioactive agent materials such as PEI & E3P nanocomposites being used to coat

The stability of biocompatibility of Q Dot can be enhanced by modifying the shell structure of Q Dot. For example, the cytotoxicity is least in CdTe/CdS/ZnS Q Dots with core- shell-shell structure. These modifications also inhibit the release of metal oxide inside the core. For example, as shown in fig (1) metal ions are released due the instability of Q Dots when a proton is dissolved, and the core shell is separated in a low pH environment such as gastric juice. From Cd-containing Q Dots, Cd^{++} ion is easily released from the core due to biodegradation or photolysis, resulting in toxicity.

We have studied other approaches to prepare Q Dots namely organic metallic synthesis and aqueous synthesis (Nan Chen 2012). It is seen that organo metallic route of synthesis of Q Dot shows excellent optical properties. For example, CdSe Q Dot with 85% high photoluminescence quantum yield (PLQY) was synthesized via organo metallic route while these Q Dots were hydrophobic in nature and cannot be directly used in bio-applications. The hydrophilic Q Dots may lead to significant increase in size and significant decrease in PLQY which hampers their

biological applications. Compared to organometallic synthesis, aqueous synthetic strategies are simple, cheaper, and more eco-friendly, but aqueous Q Dots often possess poor optical properties e.g., PLQY< 10%.

With all these applications cytotoxicity assessment of Q Dots is of critical importance for their biological and biomedical applications. It was found (Pandey V 2016) that the cytotoxicity of Q Dots was not only by nanocrystalline particle itself, but also depends on the surface covering functional groups of Q Dots for e.g., $–NH_2$ and -COOH. Assessment studies (Su Y. 2009) have been carried out to assess the systematic cytotoxicity of

CdTe/CdS/ZnS core-shell-shell structured Q Dots, the thiols – stabilized CdTe and the series of aqueous Q Dots e.g., CdTe/CdS core-shell structured materials. The cytotoxicity could be mitigated via epitaxial growth of a CdS layer to reduce the release of Cd^{++} ions.

The studies have shown that the cytotoxicity of aqueous Q Dots cannot be solely held responsible for the toxic effect of free Cd^{++} because the CdTe aqueous Q Dots were found more cytotoxic than $CdCl_2$ solutions even when the intercellular Cd^{++} concentrations were identical in the treated cells. The short- and long- term in vivo bio-distribution, pharmacokinetics and toxicity of the aqueous Q Dots effects have been observed as well. The biodistribution of aqueous Q Dots is known to be size dependent. Post injection the aqueous Q Dots are initially accumulated in liver for a period of half an hour to four hours and these are absorbed by kidney for a longer period of time which extends from fifteen to eighty days through blood circulation.

Researchers have demonstrated that certain model Q Dots for example the ZnS become more toxic as they age (Aude Bechu, 2021). The occurrence of toxicity has been reported due to the exposure of oxidative conditions of CdSe Q Dots capped with polyethylene glycol which are transformed into Cd ion and Se nanoparticles (Rzigalinski 2009). The effect of exposing Q Dots to two environmental factors**:** pH and dissolved oxygen with short (1 day) and long term (6 months) aging was also examined. The impact of pH on the chemical stability of different shells and the core that constitute the commercially relevant Q Dots were assessed and toxicity of these commercial model of pristine Q Dots and aged Q Dots in a human cell line (liver, HepG2 cells) was also studied.

In order to determine the number of solubilized ions after exposure to pH 2 to 8 as well as to atmospheric oxygen and anoxic atmospheric nitrogen systems CdSe/ZnS-PEI & E3P (CdSe / ZnS capped with a polymer polyethyleneimine reacted with epoxide) is subjected to dissolution tests. It is observed that the CdSe/ZnS-PEI & E3P Q Dots released fewer ions than comparable to CdSe/ZnS-mercaptopropionic acid Q Dots at lower concentrations (1 PPM Q Dot) under similar conditions (dark one day resolution time). While after 24 hours at pH-7, CdSe/ZnS-mercaptopropionic acid Q Dots released 30% of their Cd and that about ninety percent of their Zn and CdSe/ZnS-PEI&E3P dissolution was measured after twenty hours at pH 2 and 4 regulated by acetic acid under the dark and aerobic conditions. It is also observed that Q Dots released 0% of their Cd and 20% of their Zn. The studies also indicate a significant difference in aerobic versus anaerobic conditions occurred after six months at pH-2 for Cd. This is when approximately 65% of Cd is dissolved in aerobic conditions, but almost 100% is dissolved in anaerobic conditions. For Zn at pH3-4 dissolution, aerobic conditions cause higher dissolution after one day as compared to anaerobic conditions, but after six months there is no significant difference between aerobic and anaerobic conditions.

Conclusion

Analysis of Q Dots toxicity may be somewhat confusing because of the diversity of Q Dots being synthesized. In Q Dot core metalloid complexes, the Cadmium and Selenium are most commonly used constituents. These are rated to pose a potential harm to human health and environment because of their capabilities to cause acute and chronic toxicities in vertebrates.

From many surveys it is found that leached components from Q Dots, Cd^{++} ion and Zn^{++} ions, are the prime sources of toxicity. The reason for this is attributed to the fact that these components are leached from Q Dots upon environment weathering while the remaining aged Q Dot particles are considerably less toxic as compared to pristine

Q Dots. It was also observed that Q Dots exposed to environment relevant conditions are less toxic compared to intact pristine Q Dots while the results suggest that this decrease in toxicity to human cells is because of the lower concentration of toxic components, Cd^{++} and Zn^{++} in Q Dots. But if these Q Dots are left in the environment for long periods say six to twelve months, these are likely to release higher concentrations of toxic ions and polymer components, thus leading to more serious toxicological effects. Cd has a biological half-life of 15 to 20 years in humans, bio-accumulates, can cross the blood- brain barrier and placenta and is systematically distributed to all body tissues with liver and kidney being target organs of toxicity.

Impact of Se contamination may produce unfavorable effects on human health on the endocrine system and particularly on the thyroid gland, increase the risk of type-2 diabetes, cancers and nervous system disturbances including alterations in visual evoked potentials and excess risk of amyotrophic lateral sclerosis. Hence there is a need for studies on the environment implications of industrially manufactured Q Dots to investigate the complex interactions with capping polymers.

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