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Creation of Quantitative Feature Toxicity Relationship Models for Cytotoxicity of Cadmium Containing Quantum Dots Towards HEK Cells Using QuasiSMILES

Parvin Kumar, Kurukshetra University, Kurukshetra, India
https://orcid.org/0000-0002-2635-6465
Sunil Kumar, Guru Jambheshwar University of Science and Technology, Hisar, India
Ashwani Kumar, Guru Jambheshwar University of Science and Technology, Hisar, India*

ABSTRACT

The rising possibilities of quantum dots in biological fields have raised significant concerns about their toxicological influence, and there is a requirement of methods for prediction of toxic quantum dots. In the current research work, quantitative feature toxicity relationship models for HEK cells cytotoxicity of 41 CdSe/CdTe/CdZnS core quantum dots as a function of their size, surface ligand, ligand chemical, charge, surface modification, assay type, and quantum dot concentration have been developed. The models are constructed by using quasiSMILES representation symbolizing the experimental conditions and molecular architecture of the quantum dots. The index of ideality of correlation helps in the building of eight statistically significant, robust, and predictive models using Monte Carlo optimization. The results are used successfully for extraction of features causing an increase and decrease of cytotoxicity of quantum dots.

KEYWORDS

HEK Cells, Index of Ideality of Correlation, QFTR, Quantum Dots, QuasiSMILES, Toxicity

1. INTRODUCTION

The advancement of nanotechnology in the past decades has led to the extensive use of nanomaterials in the area of environment, energy and biomedicine (L. Hu et al., 2017). Functionalized nanomaterials like semiconductor quantum dots (QDs) are thought to be as new type of ideal fluorescent probes because of their intrinsic optical characteristics like long-term photostability, high photoluminescence quantum yields, as well as size-tunable and narrow-band emissions (Zhao et al., 2019). QDs have attracted substantial attention due to their fantastic applications in biomedical fields like bioimaging, biosensing, cancer diagnostic and drugs (L. Hu et al., 2017; Tang et al., 2008; Xu et al., 2012).

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*Corresponding Author

Their small size (1 – 10 nm) is suitable for detection and tracking of biological compounds and cell organelles inside the cell as well as in the nucleus (Filali et al., 2020).

Despite wide range of interesting applications, toxicity of QDs is a major bottleneck in their use in biomedical applications. It has been shown that QDs are cytotoxic in nature and cause dysfunction of mitochondria, cell growth inhibition, DNA impairment and apoptosis (Luo et al., 2013; Nagy et al., 2012; Wan et al., 2015). Cadmium containing QDs are reported to be toxic towards renal cells. L-cysteine-capped CdTe-QDs increase cytotoxicity and change the structure and bioactivity of copper–zinc superoxide dismutase in mouse primary nephrocytes (Trabelsi et al., 2013). Soluble CdS and ZnO QDs exhibit cytotoxic effects towards HK-2 human epithelial tubular cells in a dose dependent manner (Pujalté et al., 2015; Zhao et al., 2019). It has been reported that properties like size, surface charge, surface ligand, shell, concentration, assay type etc. influence the cytotoxicity of QDs (X. Hu et al., 2011; L. Hu et al., 2016; Rivera-Gil et al., 2013).

These facts indicate that changes in physicochemical properties of QDs can alter their toxicity (Schwarz-Plaschg et al., 2017) and thus the toxicity can be minimized during very initial phase of QDs synthesis by controlling the physicochemical parameters. Further, assessment of toxicity of QDs is very tedious and expensive task. Thus, there is requirement of applications of *in silico* alternatives for prediction of toxicity associated with QDs.

Computational techniques like quantitative structure/feature-activity/property/toxicity relationship (QSAR/QSPR/QFTR) can provide solution to the above problems (Davim & Roy, 2015). These are some of the most prominent methods used very often in the design of more effective and safer molecules (Muratov et al., 2020). In QSAR process, the structural information of the compounds is used in prediction of endpoint using some mathematical operations (Cherkasov et al., 2014). The structures of the molecules are quantitated using 1D, 2D and 3D descriptors calculated using specialized tools (Lo et al., 2018). Further, chemical reactivity descriptors such as nucleophilicity index, hardness, polarizability, compressibility, etc. are also used in constructing predictive QSAR models (Sarkar et al., 2012; Tandon et al., 2019, 2019, 2021). These are common methods for traditional substances. In case of nano materials, this classical approach has been applied but that is related with the non-nano components of the nanomaterials (Fourches et al., 2010).

Representation of chemical structure with SMILES notation has been widely used in the generation of QSAR models for different kinds of endpoints. Use of CORAL software has pioneered in these type of studies (Ahmadi et al., 2020; A. Kumar & Chauhan, 2018; Nesměrák et al., 2017; Prachayasittikul et al., 2017; Toropov et al., 2011; Veselinović et al., 2013). However, nanomaterials cannot be represented by SMILES notation as their exact chemical structure is not known. This is a major hurdle in building of QSAR models for nanomaterials. But this task can be solved by use of quasiSMILES which represents the experimental conditions and chemical constitution of the nanomaterials (Toropov et al., 2016). QuasiSMILES has been applied in making models for various endpoints related with nanomaterials (Ahmadi, 2020; Jafari & Fatemi, 2020; Toropov & Toropova, 2020; A. P. Toropova et al., 2017; Trinh et al., 2018), and the same approach can be used in creating quantitative feature toxicity relationship (QFTR) models for assessing the renal cell toxicity of QDs.

Keeping the above facts in consideration and in advancing our efforts in QSAR models development (Bagri et al., 2020; A. Kumar et al., 2020; A. Kumar & Kumar, 2020; P. Kumar & Kumar, 2020; A. Kumar & Kumar, 2021; Nimbhal et al., 2020), the present study was designed with following objectives (1) to generate quasiSMILES for QDs under study using their eclectic information (2) to construct the statistically significant QFTR models for cytotoxicity of quantum dots towards Human Embryonic Kidney (HEK) cells with these qusaiSMILES using index of ideality of correlation (IIC) in Monte Carlo method and (3) to extract the features responsible for alteration in QDs cytotoxicity towards HEK cells.

Optimal Descriptor Based QSPR Models for Catalytic Activity of Propylene Polymerization