Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 24, supplement 1, 2014, pp. 25-31

QUANTUM DOTS BASED MULTIFUNCTIONAL NANOSYSTEMS FOR THERANOSTIC APPLICATIONS

Ludmila Otilia Cinteza [1*], **Ioana Ailiesei** [2], **Sorina Petrache** [3], **Anca Dinischiotu** [3]
[1] University of Bucharest, Chemistry Faculty, Physical Chemistry Department, Bucharest
[2] University of Medicine and Pharmacy "Carol Davila" Bucharest, Faculty of Pharmacy, Bucharest.
[3] University of Bucharest, Biology Faculty, Bucharest

ABSTRACT. A facile method to obtain multifunctional nanosystems encapsulating both imaging agents and drug molecules is presented in this work. One of the modern concepts in the therapy of cancer diseases is "theranostic" (from therapy + diagnostics), that means the application of multifunctional systems to deliver the chemotherapeutic drug and the use of fluorescence agent for the imaging the treatment efficiency by monitoring the effect of the active substance on the targeted tumoral cells. The silica nanoparticles were used as matrix to encapsulate quantum dots as bioimaging agents, as they are easy to be prepared as water dispersible and stable in the physiological environment. Quantum dots from CdTe were prepared using a simple hydrothermal method, with citrate and hydrophilic polymer as stabilizer. The anticancer drug Topotecan was used as chemotherapeutic agent, coencapsulated with the semiconducting nanocrystals into the silica matrix. The complex theranostic systems were characterized by using DLS and TEM. Optical properties of the quantum dots were investigated using fluorescence spectra in various environments. The possibility to use the silica fluorescent nanosystems with Topotecan content in bioimaging was studied using fluorescence microscopy on HeLa cell culture.

Keywords: theranostic, cancer, nanosystems, quantum dots

INTRODUCTION

The main difficulty in the modern therapy is now recognized to be the lack in targeting and obtaining a suitable kinetic profile for the existing drugs. As a result, both a significant reduction of the efficiency and the presence of side effects are recorded for the majority of the active substances. For many years, the encapsulation of the drugs into various drug delivery systems seems to be the key to unlock the beneficial properties of the known chemical substances into novel pharmaceutics, with superior properties. Nevertheless, a group of diseases (such as cancer, cardiovascular, neurodegenerative disorders) there are still a major cause of mortality and still need a modern therapy.

"Theranostic" is a novel concept dealing with the integration of the diagnosis and the therapy (Warner, 2004; Sumer *et al.,* 2008). The concept is rather new, so the term is spelled in various forms, such as "theragnostic", "theranostics" or "theragnostics" (Chen, 2011). The original idea was to use multiple techniques to achieve both imaging and therapy based on multifunctional nanoparticle platforms, to obtain better results in the cancer treatment. Since in other diseases that cancer, the simultaneous diagnosis and treatment seems to be unnecessary, the theranostic concept, as it is defined in the early stage, is under debate. In the last 3 years a new definition was proposed, as the development of strategies for controlled and targeted co-delivery of diagnostic and therapeutic active substances in order to ensure the "in situ" monitoring of the treatment. The presence of the imaging agent inside the drug delivery systems (or associated with) is a valuable tool to investigate the fate of the therapeutic substance and makes possible a live surveillance of the evolution of tumor, compared to the bioavailability profile of the drug (Lammers, 2011).

The scientific ration of theranostic concept comes from the conclusion that in the case of some diseases, especially cancers, the existing treatments are effective for only limited patient groups and at selective stages of disease development. The combination of imaging/diagnosis and active substances could provide therapeutic protocols which are more specific to individuals, so paving the road to the personalized medicine.

The theranostic concept involves the administration of a complex platform with multifunctional role, containing agents for imaging (fluorescence, MRI, PET, or combination of those) and therapeutic substance. In this respect, nanotechnology provides various nanoplatforms, such as polymeric nanoparticles, micelles, liposomes, to be used as nanoplatform for co-encapsulation of the components in the theranostic approach (Deveza *et al.,* 2012; Janib *et al*, 2010).

One of the most interesting materials for the bioimaging purposes prove to be the semiconductor nanoparticles, known as quantum dots (QDs). Semiconductor nanoparticles are nanocrystals which exhibit specific optical properties when their sizes range from 1 up to 10 nm. A major advantage of QDs is the possibility to be conjugated with functional biomolecules to selectively target specific sites. Over the last decade a large variety of papers report synthesis and characterization of QDs and their use in

** Correspondence: Ludmila Otilia Cinteza, University of Bucharest, Faculty of Chemistry, Physical Chemistry Department, 4-12 Elisabeta Blvd., 030118, Bucharest, Romania, Tel. +40- (21)-3050767, Fax. +40-(21)- 3159249, email: ocinteza@gw-chimie.math.unibuc.ro*
Article received: April 2014; published: May 2014

targeted cell labeling, tissue imaging, photodynamic therapy, in vivo tumor detection, and drug delivery (Zhang *et al.*, 2012; Cinteza, 2009).

QDs have been proposed as an efficient new class of fluorescent labels for a various fields (chemical analysis, molecular imaging, biomedical diagnostics) due to their unique optical properties, superior than those of classic organic dyes. QDs are considerably brighter and more photostable, with narrow and symmetric emission spectra, and broad absorption spectra. Due to their physical properties, the semiconductor nanocrystals exhibit size-tunable fluorescent emission. The changes in size and composition could allow the development of QDs with emission in a broad range, from UV to IR (450-1400 nm). One of the most exciting application of QDs is multiplexed labeling in biology and medical area, based on their fluorescent properties, which can be tuned by simply controlling particle size and based on the possibility to simultaneously excite different nanocrystals with a single excitation light source (Bruchez *et al*, 1998; Han *et al*, 2001).

QDs with various compositions were prepared, usually CdS, CdSe, ZnS, CdTe. For biomedical use of semiconducting nanoparticles the main concern is the potential toxicity. The toxicological aspects related to the cadmium based nanoparticles are still under debate (Pelley, 2009), but because there show no significant relevance for in vitro diagnostics, QDs with Cd content for molecular diagnostics and pathology are accepted for clinically relevant application in the immediate future. For in vivo applications the requirements for the biocompatibility and lack of toxicity of QDs are more demanding (Chou *et al*, 2012). Some strategies to reduce the toxicity are the preparation of core-shell nanoparticles (CdS/ZnS or CdSe/ZnS) or to modifiy the composition by replacing Cd with Zn in composite nanoparticles (CdZnS, CdZnSe).

Since CdS and CdSe QDs were extensively studied as fluorescent agents for bioimaging, CdTe semiconductor nanoparticles were less investigated, due to the difficulty to prepare high quality nanocrystals in a facile one-pot synthesis. The CdTe based QDs recently start to be investigated as biological probes and various strategies to improve the optical properties and biocompatibility were developed (Zhang *et al.*, 2014; Xue *et al.*, 2011). The synthesis of highly luminescent and biocompatible was reported by using a core-shell-shell structure CdTe/CdS/ZnS (He et al., 2014). In the last decade alloyed quantum dots (ternary or quaternary) containing Cd, Zn, Se, Te or S, in various combinations, were investigating as new fluorescent nanoparticles suitable as useful probes for in vivo targeted imaging and clinical diagnosis. For example, CdSeTeS QDs exhibit high quantum yield (QY) up to 57.7 % , significantly long fluorescence lifetimes > 100 ns and excellent photostability. The quaternary CdSeTeS QDs linked to anti-epidermal growth factor receptor (EGFR) antibodies were used for bioimaging of SiHa cervical cancer cells (Yang *et al.*, 2013).

The encapsulation of QDs in various materials (polymers, inorganic shells such as silica) is a major route to ensure a better toxicological profile and to protect the nanocrystal from the interaction with the biological environment. The use of a suitable drug delivery system is also an important issue in the theranostic concept, thus a variety of nanoparticles was investigated as platforms to co-encapsulate the optical probe and the therapeutic agent. Nanosystems such as liposomes, polymeric nanoparticles and nanocapsules, polymeric micelles were extensively studied regarding their ability to encapsulate various diagnostic probes – organic dyes, magnetic nanoparticles, QDs, gold nanoparticles, etc., together with hydrophobic or hydrophilic drugs.

In the last decades, inorganic nanoparticles such as silica or calcium carbonates kept the attention of the scientist as potent drug delivery systems. Silica (SiO2) is a well known inorganic material, a rather large experience allow obtaining of nanoparticles with accurate size and morphology control (Tang *et al*, 2012). Silica nanoparticles can be formed by a simple process, the hydrolysis and condensation of a silane derivative, which could be either hydrophilic or organo-modified (hydrophobic), generating a large variety of synthesis procedures.

In addition, silica is considered as a safe material (Fruijtier-Polloth, 2012) regarding the interaction with the biological environment. Mesoporous silica nanoparticles were reported to be well tolerated, as demonstrated by serological, hematological, and histopathological examinations of blood samples and mouse tissues in a recent paper (Lu *et al.*, 2010), thus, provide a suitable platform for the encapsulation of chemotherapeutics or imaging agents.

In this work a rational designed novel theranostic nanosystem is developed, with minimum active elements to ensure a facile synthesis and effectiveness. The multifunctional nanoplatform is based on silica nanoparticles as "carrier" due to the simplicity in synthesis and efficient loading. The QDs are used as fluorescent imaging agent, with optical properties that were chosen to not disturb the drug molecules. Topotecan (a semi-synthetic derivative of camptothecin) was used as chemotherapeutic substance, as hydrophilic anticancer model drug. Despite Topotecan is one of the most prescribed medication in ovarian and cervical cancer, no theranostic systems were reported until now.

MATERIALS AND METHODS

Cadmium chloride anhydrous (CdCl2 ,>99%), zinc chloride (ZnCl2), 3-Mercaptopropionic acid (MPA, >98%) ammonia (30 wt %), Triton X-100, hexanol, cyclohexane were purchased from Fluka. Tetraethylorthosilicate (TEOS, >99%) and (3-Aminopropyl)triethoxysilane (APTES, >98%), tellurium powder, sodium borohydride (NaBH4 , >96

%), anhydrous 2-propanol (99.5%) were purchased from Aldrich.

The Topotecan was kindly gifted by the Actavis company.

Minimum Essential Medium with Earle's salts (MEM) and fetal bovine serum were purchased from Sigma (St. Louis MO) and Gibco.

All reagents were used as received, without further purification.

Distilled water (D-water) with resistivity of 18-25 μS was used in the preparation of all solutions. All measurements were performed at room temperature, unless specified.

Synthesis of fluorescent quantum dots:

CdTe based QDs were prepared according to a simple method reported in the literature, with minor modifications (Zhang *et. al.,* 2003; Deng *et. al.,* 2006). Briefly, the cadmium precursor solutions were prepared by mixing 0.4 mmol of anhydrous CdCl2 and 0.6 mmol of stabilizer (mercaptopropionic acid) in 100 ml of distilled water. The solution was degassed in nitrogen stream for 30 min, and freshly prepared NaHTe solution was added under vigorous stirring. The ratio Cd 2+: HTe- was 1:0.5. The NaHTe solution was prepared by reacting Te powder and NaBH4 in aqueous solution, under vigorous stirring in an oxygen-free atmosphere. The pH value of the final solution was adjusted to 6.0 by using NaOH solution (1M). The obtained mixture (20 mL) was transferred into a Teflon-lined stainless autoclave with a volume of 25 mL. The autoclave vial was maintained at 120°C for one hour and then cooled to room temperature.

The QDs were precipitated from the solution with an excess of 2-propanol and collected by centrifugation.

For the composite quantum dots CdZnTe, acertain amount of Cd precursor was replaced by zinc chloride, the rest of the procedure remains unchanged. Finally, the obtained CdTe or CdZnTe QDs were dried at room temperature under vacuum.

Synthesis of theranostic nanosystems:

The preparation of theranostic nanoplatform involves the co-encapsulation of CdZnTe quantum dots and Topotecan in silica nanoparticles in a facile one-pot procedure. The synthesis of the silica nanoparticles is performed in W/O microemulsion media in order to control the final size of the theranostic nanosystems.

The silica matrix is obtain using a simple sol-gel process using TEOS as precursor and ammonia as catalyst.

The microemulsion used as reaction media is prepared from Triton X-100 as surfactant, hexanol as cosurfactant and cyclohexane as oil, with the aqueous phase consisting in solutions of QDs and drug (Topotecan).

The dispersion of CdZnTe QDs in water was freshly prepared by stirring 5 mg of nanocrystal powder in 1 ml of distilled water and sonicating for 30 minutes in a Branson bath sonicator. A stock solution of Topotecan 5 mg/ml was prepared and used for further up-loading experiment.

Briefly, 1.77 grams of Triton X-100, 1.6 mL of hexanol and 7.5 mL of cyclohexane were mixed under magnetic stirring to form a transparent solution. Then 200 μL of aqueous Topotecan solution, and 200 μL of QDs dispersion were added, under vigorous stirring. The silane precursor TEOS was added dropwise (100 μL) and the mixture was stirred for 30 minutes at room temperature. 100 μL of aqueous ammonia was added to promote the hydrolysis of TEOS . The mixture was allowed to stir for 4 hours, followed by the addition of 10 μL of APTES for particle post-coating and surface modification. The mixture was further reacted for 1 hour. The silica particles were precipitated from the microemulsion in an excess of acetone, washed repeatedly with alcohol and water and separated by centrifugation. The supernatants were collected and subjected to analysis in order to determine the quantity of un-encapsulated Topotecan.

Characterization of quantum dots:

Ultraviolet–visible (UV–Vis) absorption spectra were measured at room temperature on a Shimazdu Mini 1240 UV–Vis spectrophotometer. Fluorescence spectra were obtained at room temperature using a Jasco spectrofluorimeter FP 8200 with the excitation wavelength of 350 nm.

Characterization of nanosystems:

Size, size distribution and zeta potential of the theranostic nanosystems were determined form DLS measurements, on a Malvern NanoZetasizer instrument.

Samples for SEM studies were prepared from silica particles dispersed in water, vortexed and sonicated for 2 minutes. Small volumes (~1−10 μL) of the silica nanoparticles suspension was placed on instrument stab without additional coating and dried overnight in a dessicator.

The microscopy investigation was performed using a FEI instrument Quanta 200.

The encapsulation efficiency of the Topotecan was determined from the amount of drug recovered during the preparation procedure. The quantification of the drug was made by using fluorescence method, the measurements were performed with a Jasco spectrofluorimeter FP 8200, with the excitation wavelength of 285 nm.

In vitro bioimaging experiments:

The human epithelial carcinoma cells (HeLa) were grown in Minimum Essential Medium with Earle's salts (MEM) supplemented with 10% fetal bovine serum. Cells were plated at a density of 2×105 viable cells/culture flask and were maintained in a humidified 5% CO_2 air atmosphere at 37°C. The medium was replaced every 3 days and the cells were subcultured after trypsinization upon reaching confluence.

For bioimaging experiments the cells were incubated for 4, 8 and 24 hours with theranostic nanoparticles at a concentration 400 μL of particles dispersion/ ml of medium.

Fluorescence imaging of cells was performed using a Zeiss inverted microscope (AxioVert A1) equipped with a CCD camera. Filter sets used were ex 350 ± 20 nm, and ex 488 ± 20 nm.

RESULTS AND DISCUSSION

A simply designed theranostic nanosystem is proposed, co-encapsulating fluorescent semiconducting nanocrystals for diagnosis and chemotherapeutic drug in the same carrier, as it is shown in figure1.

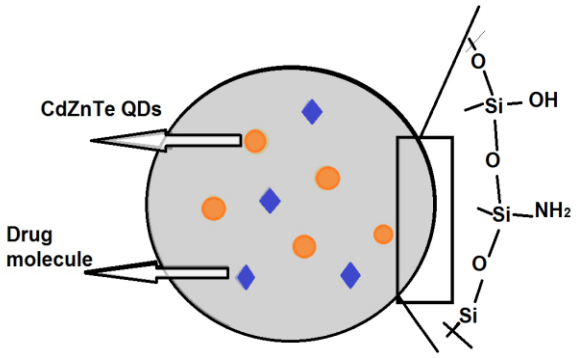


Fig. 1 Schematic view of the theranostic nanoplatform of silica matrix containing CdZnTe QDs and Topotecan as drug model.

Since the drug to be encapsulated in the silica matrix is highly hydrophilic, both the synthesis of SiO_2 nanoparticles and QDs should be adjusted to allow the encapsulation of Topotecan.

QDs with high photoluminescence are usually prepared by using organometallic routes, while aqueous synthesis results in nanocrystals with poor optical quality. Because of the difficulties on functionalization of QDs prepared in organic media to be water dispersible, a hydrothermal synthesis for the preparation of QDs was chosed, as it is described in the previous section. From the procedure used, mercaptopripionic – stabilized semiconducting nanocrystals were obtained. Since the actual Cd:Zn ratio inside the QDs is not determined we denote the composition as a mixture CdZnTe. The composition of the mixed QDs was presumed to be $Cd_{0.6}Zn_{0.4}Te$ based on the ratio of precursors used in the synthesis. Semiconducting nanoparticles with other compositions (containing Zn proportion from 0.2 to 0.5) were also successfully prepared, tuning optical properties (data unpublished).

Specific optical properties of the CdZnTe QDs dispersed in water are shown in figures 2 and 3.

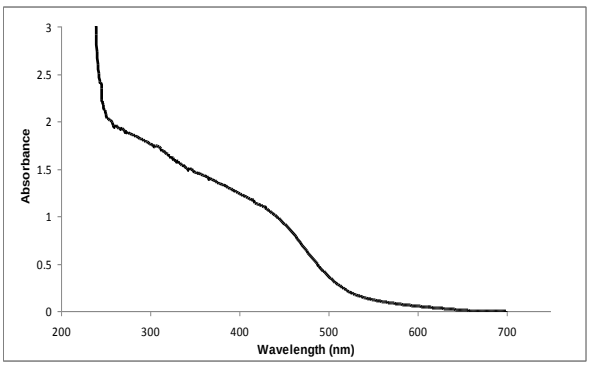


Fig. 2 UV-VIS absorption spectra of CdZnTe QDs.

The UV-VIS spectra for CdZnTe nanoparticles exhibit very high, broad range absorption, specific for the quantum dots behavior, with a shoulder around 450 nm, due to the formation of QDs. From the shape of the UV-VIS spectra one could estimate the size of nanoparticles (considering spherical shape), using Brus model (Schooss *et al.*, 1994) and physical parameters of CdTe material from Rogach (Rogach *et al.*, 1996). The band-gap energy computed from UV-VIS spectra lead to an estimation of CdZnTe nanocrystal size of 2.4 nm.

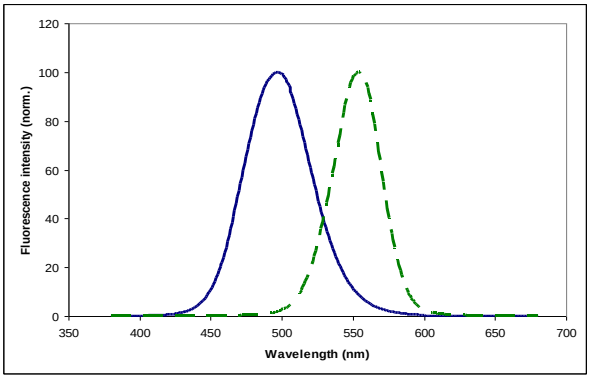


Fig. 3 UV-VIS absorption spectra of CdZnTe QDs compared to reference CdTe QDs, under 350 nm excitation wavelength.

The MPA stabilized CdZnTe QDs exhibt a maximum in the fluorescence emission at 490 nm, with a blue shifting compared to the simple CdTe QDs, as it is reported in literature (Cheng *et al.*, 2014).

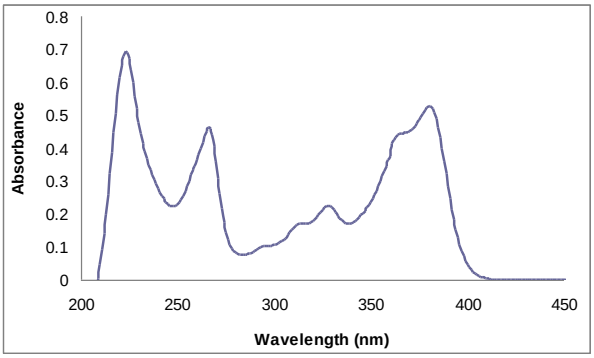
The shape of fluorescence spectra recorded for the CdZnTe dispersion in water after 48 hours of storage in normal conditions showed that QDs possessed good water solubility and monodispersity in aqueous solution.

As it is expected pure CdTe QDs exhibit a sharper peak in the fluorescence emission, suggesting a higher monodispersity compared to alloyed CdZrTe nanoparticles.

The spectral properties of the as prepared CdZnTe QDs allow the use of this type of fluorescent nanocrytals together Topotecan as drug embedded in the same matrix, since the chemotherapeutic molecule

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 24, supplement 1, 2014, pp. 25-31

exhibit different absorption zones in the UV-VIS spectra, as it is shown in figure 4a.



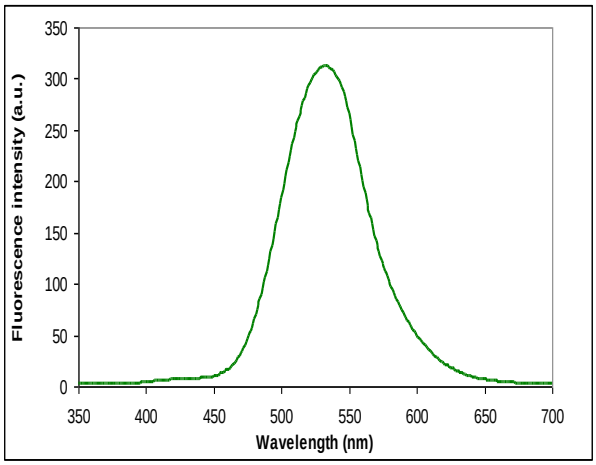


Fig. 4 The optical properties of Topotecan (a) UV-VIS spectra, (b) fluorescence spectra, excitation wavelength 285 nm.

The components of theranostic system (i.e. QDs and hydrophilic drug Topotecan were than encapsulated into the silica nanoparticles. During the synthesis of SiO_2 nanoparticles both negative and positive –charged particles were prepared, first by using ammonia as catalyst, and the other by adding a small amount of amino modified silane derivative APTES in the last stage of the reaction. The zeta potential of the un-modified silica nanoparticles was determined as -3.6 mV, while the value for the APTES-functionalized silica nanoparticles is +12.8 mV. On the basis of surface potential the particles with amino groups on the surface (APTES modified) were chosen for further experiments, due to the higher stability.

The shape of the silica nanoparticles prepared according to the method previously described is spherical, as one could observe in the micrographs in figure 5.

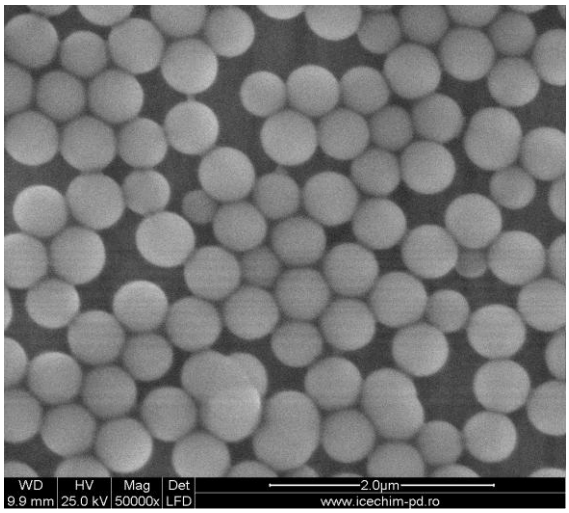


Fig. 5 The SEM images of silica nanoparticle based theranostic systems.

The size and size distribution of the silica based theranostic systems were determined from DLS measurements, showed in figure 6.

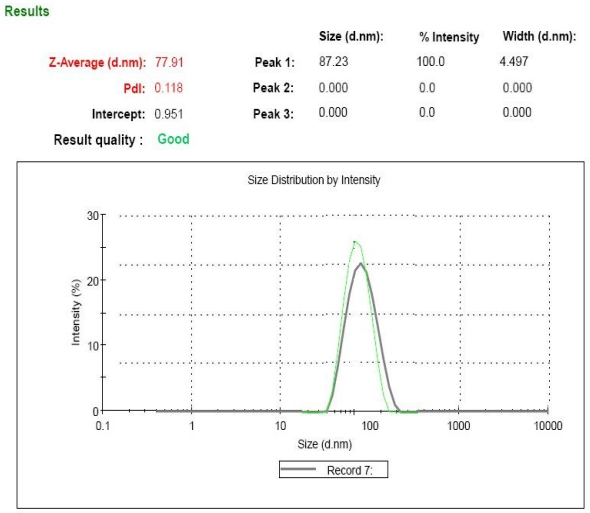


Fig. 6. The DLS graphs of void silica nanoparticles (a) and theranostic systems loaded with QDs and Topotecan, recorded immediately after preparation.

Both the void silica nanoparticles or loaded SiO_2 theranostic systems show monomodal distribution and could be considered as highly monodispersed. The presence of the QDs and drug molecules co-encapsulated into silica nanoparticles does not change the average size of final theranostic system.

The monodispersity of the theranostic system is preserved during six week of storage, as dispersion in distilled water, since the average size of the silica particles does not significantly changes (from 87 nm to 90 nm) and only a small amount of aggregates appears (around 1000 nm, probably due to the aggregation of original nanoparticles). The aggregates are disrupted under a moderate stirring under sonication for 5 minutes.

The encapsulation efficiency for the active ingredients QDs and Topotecan was evaluated by measuring the supernatant solutions resulted during the purification of silica loaded nanoparticles. The UV-VIS and fluorescence spectra obtained under excitation at 350 nm does not reveal the presence of QDs into the supernatant, thus the entrapment of rather total quantity of the CdZnTe nanoparticles inside the silica matrix could be considered.

The situation is different for the drug, the small hydrophilic molecule is much difficult to be encapsulated in a high extent. Based on a fluorescence analysis of Topotecan in aqueous, acetone and alcoholic supernatants an average 62% efficiency of the encapsulation for the drug into silica nanoparticles was found.

The possibility to use the prepared theranostic system for bioimaging using fluorescence microscopy was investigating. In the figure 7 microscopy images are shown obtained with HeLa cells incubated with the theranostic systems based on CdZnTe QDs as imaging fluorophores.

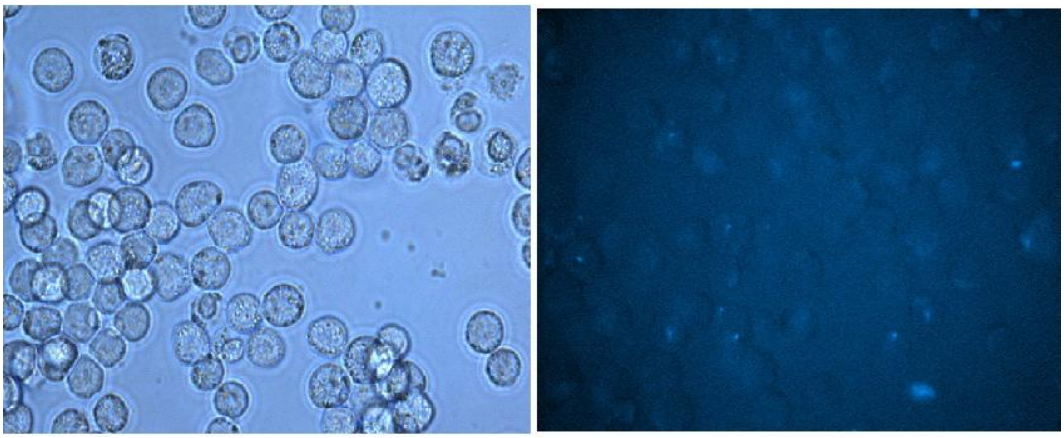


Fig. 7 The microscopy images of HeLa cells incubated for 12 hours with theranostic nanosystems based on CdZnTe QDs. Filter used 350/20 nm excitation.

The bright spots in the picture under UV excitation correspond to QDs in the theranostic nanoparticles, large size of it suggesting that aggregation occurs during the incubation due to the interaction with cells and components from the medium.

CONCLUSIONS

In summary, the hydrothermal approach was used as a facile route to synthesize high-quality MPA-stabilized CdZnTe QDs, with good optical properties. The as prepared fluorescent nanoparticles were successfully co-encapsulated together Topotecan as hydrophilic model chemotherapeutics inside a silica matrix.

The preparation of SiO_2 nanoparticles as carrier for the therapeutic active components proves to be a good choice, due to the stability, facility in surface functionalization and encapsulation efficiency.

The *in vitro* test of cellular imaging also suggests that the proposed theranostic nanoplatform could be used for the detection of tumor cells. Further work is needed to study the in vitro and in vivo effect of Topotecan embedded in the theranostic containing CdZnTe QDs.

ACKNOWLEDGMENTS

We thank the National R&D Institute for Chemistry and Petrochemistry ICECHIM, Bucharest for the help with SEM measurements.

REFERENCES

Bruchez MP, Moronne M, Gin P, Weiss S, Alivisatos AP, Semiconductor nanocrystals as fluorescent biological labels, Science, 281, 2013–2016, 1998.

Chen XS, Introducing Theranostics Journal, Theranostics, 1, 1-2, 2011.

Cheng J, Li D , Cheng T, Ren B, Wang G, Li J, Aqueous synthesis of high-fluorescence CdZnTe alloyed, Journal of Alloys and Compounds, 589, 539–544, 2014.

Chou LYT, Chan WCW, Nanotoxicology: No signs of illness, Nature Nanotechnolgy, 7, 416-417, 2012.

Cinteza LO, Quantum dots in biomedical applications: advances and challenges, J. Nanophoton. 4, 042503 , 2009.

Deng DW, Qin YB, Yang X, Yu JS, Pan Y, The selective synthesis of water-soluble highly luminescent CdTe nanoparticles and nanorods J. Cryst. Growth, 296, 141–149, 2006.

Deveza L, Choi J, Yang F, Therapeutic angiogenesis for treating cardiovascular diseases, Theranostics 2, 801-814, 2012.

Fruijtier- Polloth C, The toxicological mode of action and the safety of synthetic amorphous silica-a nanostructured material, Toxicology, 294, 61-79, 2012.

Han M, Gao X, Su JZ, Nie S, Quantum-dot-tagged microbeads for multiplexed optical coding of

biomolecules, Nat. Biotechnol., 19, 631–635, 2001.
He H, Sun X, Wang X, Xu H, Synthesis of highly luminescent and biocompatible quantum dots using microwave irradiation: a comparative study of different ligands. Luminescence, doi: 10.1002/bio.2630, 2014.
Janib SM, Moses AS, MacKay JA, Imaging and drug delivery using theranostic nanoparticles, Adv Drug Deliv Rev., 62, 1052-1063, 2010.
Lammers T, Aime S, Hennik WE, Storm G, Kiessling F, Theranostic Nanomedicine, Acc. Chem. Res., 44 , 1029–1038, 2011.
Lu J, Liong M, Li Z, Zink J, Tamanoi F, Biocompatibility, Biodistribution, and Drug-Delivery Efficiency of Mesoporous Silica Nanoparticles for Cancer Therapy in Animals, Small, 6, 1794–1805, 2010.
Mai WX, Meng H, Mesoporous silica nanoparticles: A multifunctional nano therapeutic system, Integr. Biol., 5, 19-28, 2013.
Pelley JL, Daar AS, Saner MA, State of Academic Knowledge on Toxicity and Biological Fate of Quantum Dots, Toxicological Sciences, 112, 276–296, 2009.
Rogach AL, Katsikas L, Kornowski A, Su D, Eychmuller A, Weller H, Synthesis and Characterization of Thiol-Stabilized CdTe Nanocrystals, Ber. Bunsenges. Phys. Chem., 100, 1772-1778, 1996.
Schooss D, Mews A, Eychmuller A, Weller H, Quantum-dot quantum well CdS/HgS/CdS: Theory and experiment Phys. Rev. B,49, 17072, 1994.
Sumer B, Gao J, Theranostic nanomedicine for cancer, Nanomedicine (Lond), 3, 137-140, 2008.
Tang F, Li L, Chen D, Mesoporous Silica Nanoparticles: Synthesis, Biocompatibility and Drug Delivery, Adv. Mater., 24, 1504–1534, 2012.
Warner S, Diagnostics plus therapy = theranostics, Scientist 18, 38-39, 2004.
Xue M, Wang X, Wang H, Tang B, The preparation of glutathione-capped CdTe quantum dots and their use in imaging of cells, Talanta 83, 1680-1686, 2011.
Yang F, Xu Z, Wang J, Zan F,Dong C, Ren J, Microwave-assisted aqueous synthesis of new quaternary-alloyed CdSeTeS quantum dots and their bioapplications in targeted imaging of cancer cells. Luminiscence, 28, 392-400, 2013.
Zhang C, Yan J, Liu C, Ji X, He Z, One-Pot Synthesis of DNA-CdTe:Zn(2+) Nanocrystals Using Na2TeO3 as the Te source, ACS Appl Mater Interfaces, 6, 3189-194, 2014.
Zhang H, Zhou Z, Yang B, Gao M, The influence of carboxyl groups on the photoluminescence of mercaptocarboxylic acid-stabilized CdTe nanoparticles, J. Phys. Chem. B, 107, 8–13, 2003.
Zhang Y, Wang T-H, Quantum dot enabled molecular sensing and diagnostics, Theranostics, 2, 631-654, 2012.