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Tailoring folic acid and methotrexate-attributed quantum dots for integrated cancer cell imaging and therapy

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Tailoring Folic acid and Methotrexate-attributed Quantum Dots for Integrated Cancer Cell Imaging and Therapy

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Abstract. Potential application of folic acid and methotrexate-attributed AgInS2-ZnS quantum dots on both detection and therapeutic of cancer cell were intensively investigated on this study. In the initial step, the bright luminescent of QDs, with % QY up to 55.3, were synthesized with one-pot two-step process resulting narrow particle distribution and successfully transferred to water phase without significant effect on optical properties. The water-soluble AgInS2-ZnS quantum dots (QDs) encapsulated with oleylamine have been successfully prepared by ultrasonication assisting. Several aspect including QDs characterization, pH stability, ionic strength, and bonding properties were investigated to reach desired condition of water-soluble AgInS2-ZnS QDs. Folic acid was further conjugated to QDs for HeLa and MCF7 cancer cell imaging to performs the targeting capability. Moreover, folic acid is efficiently internalized into cell through the receptor-mediated endocytosis even when conjugated with a wide variety of molecules. Confocal imaging characterization further informs folic acid-conjugated AgInS2-ZnS QDs could most specific targeted to the human cervical (HeLa) cells. The therapeutic feature of QDs on HeLa cancer cell was conjugated by attributing methotrexate on the QDs, instead of folic acid, and the design could improve on inhibiting the cancer cell viability as well as its fluorescent intensity.

1 Introduction

The application of functional nanoparticles (NPs) in biomedicine has been extensively developed, and nominated as one of the rapid improving and fascinating research directions.[1, 2]Up to now, severalNPs; like, silicon nanowires, carbon nanotubes, gold/silver NPs, quantum dots (QDs) etc., have been promoted widespread in biological applications, especially on handling cancer disease.[3-5] Among those of used NPs, photofluorecent Quantum dots (QDs), as a type of high-performance bioprobes,are attractive and the foremost on nano-biotechnology research. QDs,also referred as semiconductor nanocrystals, are single crystals with order nanometers in its diameter. This materials showed advantage that is more promising compared to conventional fluorescent bio-probes (organic dyes and fluorescent proteins), including high photoluminescence quantum yield (PLQY), broad absorption coupled with narrow emission, and strong photo-stability.[6, 7]

Recently, how to design nontoxic QDs and the way to get high performance QDs are two important key for applying its material on biomedical fields. Synthesis of I-III-VI nanocrystals QDs, like $AgInS_2$ QDs, was one ofmost appropriate strategy on overcome toxicity problems in QDs application. Moreover, next efforts to increase photoluminescence have been focused including coating strategy on the bare particle.[8-10]Synthesis way on obtaining hydrophilic QDs became further problem the application due to only material with highly water solubility that can facilely applied on biological application. In many study on synthetizing $AgInS_2$, organic-based synthesis process was preferred to obtain high monodispersity and excellence photoluminescence.[11, 12] Therefore, the strategy on phase transfer process of material was quite important and paying a challenge for researchers so far. It was well documented that several phase transfer method was intensively developed, such modifyingQDs with long sequence surfactant, like proteins,[13-15]biological molecules,[16] DNA,[17, 18] and polymer.[19, 20]This strategy potentially emerges problematic degradation on optical properties caused by aggregated QDs. To overcome these issues, alternatively phase transfer protocols was promoted by applying small surfactant for ligand exchange and double layered formation on surface of QDs.[21-24]On these cases, adjusting small surfactant, as second layer of QDswas more preferred related to widely chance of interaction to target and protection serviced from harm reaction.[23, 25]

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In our previous, publication we design phase transfer strategy by using carboxylate based surfactant and deeply improved its potency on providing good stability, toxicity, staining ability along with its benefits of cancer drug delivery.[3, 10] Carboxylate site as new face of transferred QDs take important key on next step reaction process, influence the mechanism drug loading, andaffecting the colloidal stability that little bite move on base.However, intracellular circumstances became more acid when up-taking new material out site due to particular process of endosomes/lysosomes compartments.[26] Based on this consideration, we further develop in here a simple and effective phase transfer strategy of QDs assisted byoleylamine followed by the observation on its potency on cancer detection and therapyare exploited after its chemical conjugation with folic acid (FA) and methotrexate (MTX).

2 Experimental Section

2.1 Materials

Zincstearate(90%),1-dodecanethiol(DDT,97%),1-octadecene(ODE,90%), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT, 97.5%), N-hydroxysulfosuccinimidesodiumsalt(NHS,>97%),4'-6-diamidino-2-phenylindole(DAPI,>98%), andpotassium ethylxanthate(90%)werepurchasedfrom Sigma-Aldrich(Milwaukee,USA).Indiumacetate (InAc,99.98%), silveracetate (AgAc,99%),decanoicacid(99%),and*n*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide(EDC,99%)werepurchased from Alfa-Aesar(Ward Hill, USA).Zincchloride (90%)was purchased from Riedel-deHaënAG (Seelze,Germany). Folate (>98%)was purchasedfrom T.C.I.ChemicalCo.(TCI,Japan). Oleylamine(80–90%)werepurchased fromAcrosOrganics (Geel, Belgium). All chemicalswere used directlywithoutfurtherpurification.

2.2 Synthesis of $AgInS_2$-ZnS QDs

The synthesis process of QDs followed previous publications.[10]Briefly, the specific amount of AgAc, InAc,DDT and ODE were mixed into reaction container attributed with a condenser and thermocouple line. Under magnetic stirring, the mixture was heated at 220 °C for 30 min under argon flow. The injection solution of the ZnS precursor was dropwise added by means of a syringe pump (KD Scientific KDS100, USA) at rate 0.13 mL min^{-1}. After the injection was complete, the reaction mixture was cooled to room temperature, followed by centrifugation at 6000 rpm for 20 min. The supernatant was collected and washed in 5 mL chloroform and 7.5 mL methanol for three times and precipitatedfor next step.

2.3 Encapsulation of $AgInS_2$-ZnS QDs by Oleylamine (OA@QDs)

Around 40 mg $mL^{-1}$of QDs was firstly dissolved in hexane and mixed with oleylamine (0.252 mmol) and 10 mL of 2-(*N*-morpholino)ethanesulfonic acid (MES) buffer solution (pH 7.4) was added. Ultrasonicatorprobe was further immersed on the mixture for 2 minutes for accelerate capsulation process. The mixture was centrifuged (on 6000 rpm, 10 mins) and the aquose phase then collected. Then, this solution was extracted and passed through 0.22 μm filter to separate the aggregated QDs. In the final stage, the dialysis process with a polyethersulfone membrane (MWCO 3000 Da; Cellu Sep H1, Orange Scientifique, Belgium) was further conducted to remove excess alkyl-capping ligands by tangential ultrafiltration.

2.4 Preparation of MTX and/or FA-QDs

Conjugation of FA on the QDs was initiated by activation carboxylate-site of FA. In particularly, FA (0.05 mmol) dissolved in MES buffer (20 mL) was added with 0.13 mmol of EDC and 0.17 mmol of NHS followed by mixing process at room temperature for 30 min under. The solution was then mixed with QDs solution and stirred gently for 24 h at room temperature in the dark. Purification on this stage was be done by centrifuge process at 10,000 rpm for 10 min and washed three or four times with MES (pH 7.4). Procedure above was also implemented to prepare MTX-OA@QDs by replacing FA with MTX (0.05mmol). Combination FA and

MTX (MTX-FA-OA@QDs) also use same procedure with simultaneously mixing both 0.05 mmol of FA and MTX on 20 mL MES buffer.

2.5 Toxicity Study with MTT Assay

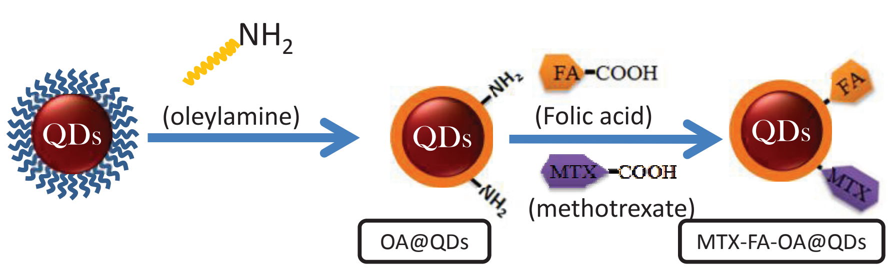
HeLa cell cultured at 24 h was carried out to MTT (Thiazolyl blue tetrazolium bromide) tests, which used to evaluate the viability and itscell activity. In the first step, the cultured cells were washed with PBS for three times, and 1 ml MTT solution (0.1 mg/ml) was added into the culture dishes for 4 h at 37 °C. Then, the resulted formazan dyes was dissolved by DMSO solution and quantified by using ELISA reader at a wavelength of 570 nm.

2.6 Cell Culture and Observation of Intracellular Location of QDs with Confocal Microscopy

The HepG-2, HeLa and MCF-7 cells were cultured in Eagle's Minimum Essential Medium (containing 1.5 g/L sodium bicarbonate) supplemented with 1% L-glutamine, 1% antibiotic anti mycotic formulation, and 10% fetal bovine serum. To induce cell expansion and senescence, the cells were cultured in a humidified 5% CO_2 atmosphere at 37 °C. HepG2 cells were seeded in a six-well plate in 2 mL of culturing medium 24 h before QDs feeding. After 1 h of incubation with 300 μL of QDs, the cells were washed three times with phosphate buffered saline PBS and then fixed with 75% alcohol for 10 min. Then, the fixed cells were incubated for 20 min at room temperature with 2 mL (0.05 μg/mL) DAPI in PBS for nucleus staining. Fluorescence images were acquired by confocal laser scanning microscopy.

2.7 Characterization

X-ray diffraction (XRD) samples were prepared by depositing the nanocrystals on a Si(100) wafer; XRD measurements were performed were investigated by a Rigaku 18 kW rotating anode source X-ray diffractometer with the Cu $K_{\alpha 1}$ line (λ = 1.54 Å). High Resolution Transmission Electron Microscopy (HRTEM) samples were prepared by dropping a dilute solution of QDs on carbon-coated copper grids (Formvar/Carbon 300 Mesh) and by slowly evaporating the solvent in air at room temperature. The ultrastructure of the nanocrystals was examined by field-emission TEM on a Philips Tecnai G2 F20 microscope (Philips, Holland), quipped with an energy-dispersed X-ray (EDX) detector operated at an accelerating voltage of 200 kV. UV-vis absorption spectra were measured with a JASCO V-670 spectrometer. The measurements of PL spectra were carried out by using a JASCO FP-6500 spectrofluorometer equipped with a 150 W xenon lamp. The PL QY of various samples were comparatively studied by taking rhodamine 6G (R6G) as a reference fluorescent dye with the known QY (95%) and comparing the integrated fluorescence intensity of the solutions, both recorded exciting samples having the same absorbance (< 0.1 a.u. in order to minimize possible re absorption effects). This method has been discussed extensively elsewhere. The PL QYs of the as-prepared QDs were calculated using the following equations: $QY=QY_{R6G}\ I_{QD}/I_{R6G}(\eta_{chloroform}/\eta_{ethanol})$ where I and η denote the integral PL intensity and the optical density and reflective index of the solvent, respectively. Fourier transform infrared (FTIR) spectra were acquired using a Bio-Rad FTS-3500. Dynamic light scattering (DLS) data was collected using a Malvern instrument ZetasizerNanoseries 3000 HS with He/Ne at 13° scattering angle. Cells imaging was performed on a Leica TCS SP2 inverted confocal microscope (Leica Microsystems) equipped with a 63×1.32 NA oil immersion. Images were obtained by illuminating the samples with the inline Ar (488 nm) and He-Ne (543, 633 nm) lasers of the microscope and with a 405-nm violet laser.



SCHEME 1. Synthesis route of MTX-FA-OA@QDs

3 Result and Discussions

3.1 Synthesis and characterization of OA@QDs

This study promote application of $AgInS_2$-ZnSQDs which promising high photoluminescence emission and acceptable on toxicity properties as well. The synthesis process conducts on the sustainable process, so call one-pot two steps process, including core formation ($AgInS_2$) and ZnS coating. The process refers on previous studies that were also validated on the size, chemical structure, and composition.[3, 10, 15]The synthesis process was designed to obtain hydrophobic stage by attributing hydrocarbon part of DDT as new face of QDs. The synthesized QDs were further phase transferred by particular energy wave provided by ultrasonication probe. By existence of oleylamine, ultrasoundwill form water bubbles with hexane inside as solvent of both QDS and oleyamine. This acoustic waves alsocauseharmonically compression and expansion on the transmitting medium.[27]When the bubbles be compressed on small enough, oleylamine inside would self-orienting to form hydrocarbon capsulated QDs and its amine siteexpose on the upper face of QDs, as shown of **scheme 1**.

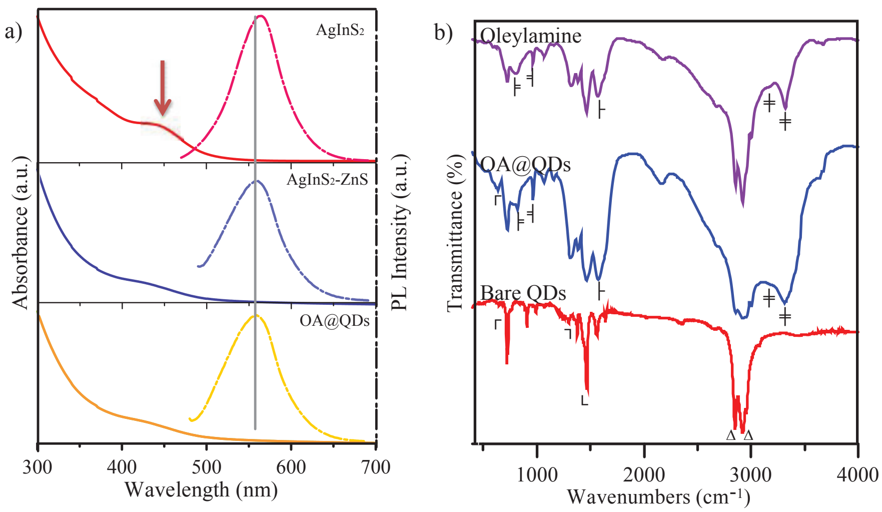


FIGURE 1.UV-vis absorption and PL (λex = 430 nm) spectra of (a) AgInS2 QDs, (b) AgInS2-ZnS, and OA@QDs. The red array indicates the excitonic absorption peak.b) FTIR spectra of (a) pristine QDs, DA/QDs, and bare oleylamine.

Arrangement of oleylamine to form encapsulated QDs was mainly belong to physical interactions, including van der Wall, electrostatic and hydrogen bonding; this system was proved a safety way to delivering QDs to water phase. UV-Vis absorption study was noticed that the strategy maintainsphotoluminescence of QDs very well, as showed on **Fig. 1a**, which slightly decrease %QY of QDs from 55.3 to 40.5. The consistently exciton peak (around 400-500 nm) that which indicated insignificantirradiative recombination at the surface sites of QDs, still appeared after transferring process. Also, the maximum peak of PL emission (PL λ_{max}) for OA@QDs in the water phase is 555 nm was similar with it was on initial QDs. The shifting position of PL emission to the lower wavelength, so call blue shift, has performed while ZnS introduce to $AgInS_2$. This condition was close-related to ZnS inter-diffusion (3.91 eV) into a narrower $AgInS_2$band gap (1.87 eV).[28]Moreover, vibration studies comparing QDs and OA@QDs are furnishedon**Fig. 1b**.On spectrum of OA@QDs thatpromoting encapsulation oleylamine on the surface of bare QDs, it is easy to finda broad band in between 3100 and 3380 cm^{-1}(╪) which can be assigned to stretching peak of aliphatic NH_2. The amine vibration at 748 cm^{-1}(╞) are both observed in OA@QDs and oleylamine. The C–N stretching vibration is also observed between 1000 and 1200 cm^{-1}(╡). Thus, a band at 1680 cm^{-1} for OA@QDs(├) and oleylamine attributing to C=C stretching mode, it was not observed in the spectrum of bare QDs. These data show qualitative information on facile encapsulation capability on the surface of QDs forming OA@QDs.

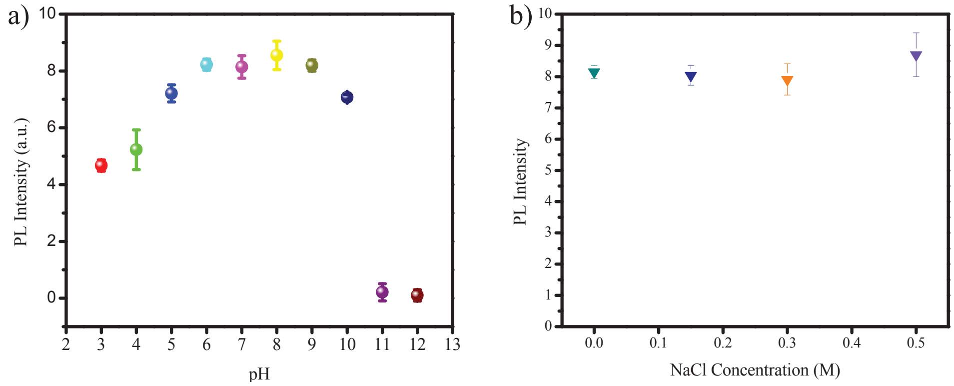


FIGURE 2.a) Graph of OA@QDs on aqueous solutions of varied pH (from 3 to 12). b) Graph of OA@QDs against 0 M (1), 0.15 M (2), 0.3 M (3), and 0.5 M (4)of NaClconcentration. All data performed after 24 h.

Further investigation was focused on adjusting colloidal stability of OA@QDs. In here, stability of QDs against varied pH and salt was under concern due to its application on biomedical field. In human body, compartment of organism can raise particular pH value apart salt concentration, for instance on pancreatic region around pH 8 and intracellular lysosomes is around 4–5.[30, 31]Therefor, the designed QDs must show well stability on the pH range. Data on **Fig. 2** furnished elegantly the emission of OA@QDs can still maintained onto pH range 3-12. However, OA@QDs shows pH stability on range 3-10 until 24 h.

3.2 Potency on Cancer Imaging and Drug Delivering

To investigate capability of OA@QDs on cell targeting, FA was proposed to be conjugated on colloidal QDs. Huge existence of folate receptor (FR) on many kind of cancer compared on healthy cells and its high affinity with FA (K_D ~100 pM) make FA as good candidate for delivering QDs onto intracellular of cancer cell.[18] In this study, FA was covalently bonded with OA@QDs through EDC/NHS reaction. As described on scheme 2 above, OA@QDs manifest amine as upper site on water phase, which easily reacts with activated carboxylate site of FA after formation succinimidyl intermediate (**Scheme 2**). Conjugating FA onto OA@QDs further called FA-OA@QDs. The biocompatibility evaluations of FA-OA@QDs on cellular uptake were performed with confocal laser-scanning fluorescent microscopy(**Fig. 3**). After 1 h incubation, FA-OA/QDs was found on cytoplasm of human cervical (HeLa) cancer cells and human breast (MCF7) cancer cells. However, compared with MCF7, fluorescence of FA-OA@QDs on HeLa show was brighter. The large number of folate receptor has been predicted to be responsible for these phenomena because folate receptor on HeLa membrane was higher than HepG2 and MCF7. [19] To ensuringthe effect FR on receptor-mediated endocytosis of QDs, Confocal image of HeLa cell after 1 h incubation with OA@QDs was also furnished on **Fig 3a-d**. Without FA as cancer targeting, QDs did not show significant emission on cytoplasm of cell even QDs still possible to penetrate on the cell with macropinocytosis (nonspecific uptake, not mediated by receptors).[20]These clearly reveals that FA in the surface of QDs are plays important role onaccelerating receptor-mediated endocytosis of QDs.

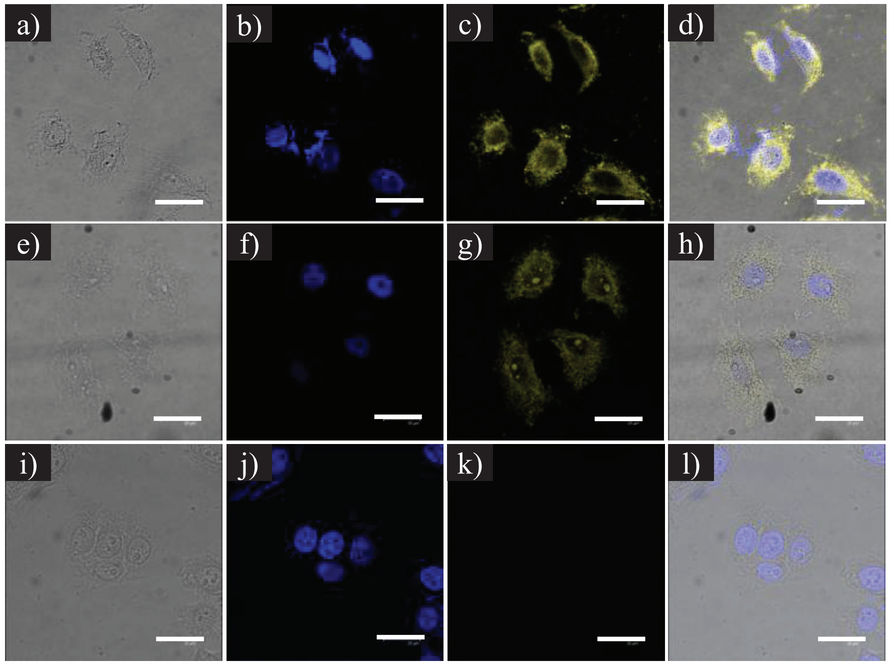


FIGURE 3. Confocal images of HeLa cells(a-d) and MCF7 cells (e-h) stained with a solution of FA-OA@QDs and OA@QDs (i-l). The figures composed (from left to right) : Optical images of cells under visible light, DAPI emission at 460 nm, yellow fluorescence originating from QDs, and its composite image. Scale bar showed 20 μm.

Potential application of the QDs on MTX drug delivery was reveal by toxicity study using MTT assay. MTX thatcommonly used as cancer drug, is analog structure of FA along with convenient on cell internalization through FR.[21] Thus, MTX performs simultaneous function on cancer drug and targeting ligand. Like FA, MTX also have glutamaic acid cite that make it possible to be conjugated with OA@QDs via EDC/NHS reaction (**Scheme 2**). Beside to evaluate the cytotoxicity, MTT assay can also performsthe efficacy of addition MTX on OA@QDs on targeted cell. In its working ways, the absorbance of formazan (produced by cleavage of MTT by dehydrogenases in living cells) at 570 nm is directly proportional to the number of live cells. Due to MTX was as low-act drug process that induces cell death by starvation.Cytotoxicity investigation was done by incubating OA@QDs, FA-OA@QDs, and MTX-FA-OA@QDs into HeLa cell for 48 h. It was demonstrated on **Fig 4** that amount of living cell still over 80% after 48h incubated with OA@QDs. The phenomena show similarities even concentration was increased up to 300 μg/mL. Interestingly, the FA-OA@QDs also performs similar results, which indicate both QDsdoes not have innocuous effect on living cells. However, after conjugating wit MTX, QDs showed significantdecreasing of living cell and the affect on cell was in line with enhancing concentration of FA-OA@QDs. This *in vitro*study clearly implies that the QDs have great change as cancer staining and drug delivery agents as well.

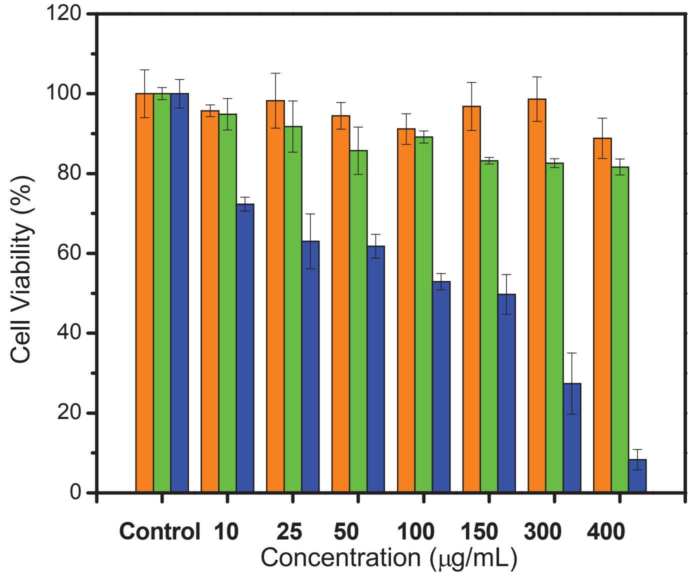


FIGURE 4. *In vitro* viability of HeLa cell incubated for 24 h at 37 ºC with various concentration of OA@QDs (orange bars), FA-OA@QDs (green bars), and MTX-FA-OA@QDs (blue bars).

4 Conclusions

A simple and facile phase transfer technique to provide water soluble $AgInS_2$-ZnS QDs has been described. ZnS coating on $AgInS_2$ QDs has a smart choice for both QDs support and enhance the optical properties of $AgInS_2$ QDs. The sonication wave quite powerful on arranging oleylamine to be self-assembly on surface of QDs. Notably, associating of both FA and MTX is good way to optimizing potential of water soluble QDs on cancer targeting as well as MTX delivery.The covalent conjugation of FA accelerates QDs on cell internalization into HeLa cancer cell *via* folate receptor-mediated targeted delivery as compared with MCF-7 cancer cells. Further conjugation of MTX, beside FA, on DA/QDs gave advanced application as a targeting ligand as well as a cytostatic agent.

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PRELIMINARY

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BIODIVERSITY

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AIP Conference Proceedings 1718, 030001 (2016) doi: https://doi.org/10.1063/1.4943311

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The influence of dicarboxylic acids: Oxalic acid and tartaric acid on the compressive strength of glass ionomer cements

Ahmadi Jaya Permana; Harsasi Setyawati; Hamami; Irmina Kris Murwani

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The effect of glicerol and sorbitol plasticizers toward disintegration time of phyto-capsules

Pratiwi Pudjiastuti; Esti Hendradi; Siti Wafiroh; Muji Harsini; Handoko Darmokoesoemo

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Speciation and bioavailability of some heavy metals in agricultural soils used for cultivating various vegetables in Bedugul, Bali

I. Made Siaka; I. Made Supartha Utama; I. B. Putra Manuaba; I. Made Adnyana; Emmy Sahara

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Potential contribution of low cost materials in clean technology

Heman A. Smail; Kafia M. Shareef; Zainab Ramli

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Monitoring of coastline change using remote sensing data at South Pamekasan

Thin Soedarti; Onny Z. Rinanda; Agoes Soegianto

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The production of sulfonated chitosan-sodium alginate found in brown algae (*Sargassum sp.*) composite membrane as proton exchange membrane fuel cell (PEMFC)

Siti Wafiroh; Pratiwi Pudjiastuti; Ilma Indana Sari

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Virtual screening using MTiOpenScreen and PyRx 0,8 revealed ZINC95486216 as a human acetylcholinesterase inhibitor candidate

Sulistyo Dwi K. P.; Arindra Trisna W.; Vindri Catur P. W.; Erna Wijayanti; Mochammad Ichsan

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Three-step crystallization in synthesis of ZSM-5 without organic template

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Spermatogenic structure and fertility of *Mus musculus* after exposure of mangosteen (*Garcinia mangostana L*) pericarp extract

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Double layer structure-based virtual screening reveals 3'-Hydroxy-A-Naphthoflavone as novel inhibitor candidate of human acetylcholinesterase

Mochammad Ichsan; Ardini Pangastuti; Mohammad Wildan Habibi; Kartika Juliana

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Total flavonoid and phenolic contents of n-butanol extract of *Samanea saman* leaf and the antibacterial activity towards *Escherichia coli* and *Staphylococcus aureus*

Wiwik Susanah Rita; I. Made Dira Swantara; I. A. Raka Astiti Asih; Ni Ketut Sinarsih; I. Kadek Pater Suteja

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Phenolic compounds from the stem bark *Erythrina Orientalis* and detection of antimalaria activity by *ELISA*

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Morphology characterization and biocompatibility study of PLLA (Poly-L-Llactid-Acid) coating chitosan as stent for coronary heart disease

Prihartini Widiyanti; Adanti W. Paramadini; Hajria Jabbar; Inas Fatimah; Fadila N. K. Nisak; Rahma A. Puspitasari

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Preparation and characterization Al^{3+}-bentonite Turen Malang for esterification fatty acid (palmitic acid, oleic acid and linoleic acid)

Abdulloh Abdulloh; Nanik Siti Aminah; Triyono; Mudasir; Wega Trisunaryanti

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Electrochemical degradation of malachite green using nanoporous carbon paste electrode

Muji Harsini; Faizatul Fitria; Pratiwi Pudjiastuti

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Potential complex of rhodamine B and copper (II) for dye sensitizer on solar cell

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Gas chromatography-mass spectrometry of ethyl palmitate calibration and resolution with ethyl oleate as biomarker ethanol sub acute in urine application study

Ni Made Suaniti; Manuntun Manurung

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Isolation, transformation, anticancer, and apoptosis activity of lupeyl acetate from *Artocarpus integra*

Hery Suwito; Wan Lelly Heffen; Herry Cahyana; Wahyudi Priyono Suwarso

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Forward problem solution as operator of filter and back projection matrix to reconstruct the various of data collection in electrical impedance tomography

Khusnul Ain; Deddy Kurniadi; Suprijanto; Oerip Santoso; R. Arif Wibowo

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Saeed O. Ibrahim; Bassam M. Mustafa

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Size dependence lattice thermal conductivity for Si nanofilm

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Estimation of median growth curves for children up two years old based on biresponse local linear estimator

Nur Chamidah; Marisa Rifada

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An implementation of continuous genetic algorithm in parameter estimation of predator-prey model

Windarto

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Chlorophyll mediated photodynamic inactivation of blue laser on Streptococcus mutans

Suryani Dyah Astuti; A. Zaidan; Ernie Maduratna Setiawati; Suhariningsih

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Nearest patch matching for color image segmentation supporting neural network classification in pulmonary tuberculosis identification

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Infant breathing rate counter based on variable resistor for pneumonia

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