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A new approach to highly sensitive determination of retinoic acid isomers by preconcentration with CdSe quantum dots

Behzad Torabi, Farzaneh Shemirani *

Department of Analytical Chemistry, University College of Science, University of Tehran, P.O. Box 14155-6455, Tehran, Iran

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ABSTRACT

Unusual amounts of retinoic acid (RA) isomers play an important role in abnormal morphological development of mammals; such as rat embryos. Each isomer of RA has a unique function in first steps of embryonic life. In the current study, a new method for preconcentration and simultaneous determination of *all-trans* retinoic acid, 13-*cis* retinoic acid, 9-*cis* retinoic acid and 9,13-*di-cis* retinoic acid in rat whole rudimentary embryo culture (RWEC) has been developed. RA isomers were extracted from samples by conjugation to appropriate amount of surface modified CdSe quantum dots (QDs) prior to HPLC/UV determination. In order to quickly release of the analytes with unchanged form, separated RA–QD conjugation were irradiated by intensive near infrared wavelength (NIR). Low energy NIR irradiation results in maintaining the primary forms of RA isomers during the release. The conjugation and release mechanisms were described and experimental parameters were investigated in detail. Under optimized conditions, the method was linear in the range of 0.040–34.600 pmol g^{-1} for *all-trans* RA (R^2=0.9996), 0.070–34.200 pmol g^{-1} for 13-*cis* RA (R^2=0.9992), 0.050–35.300 pmol g^{-1} for 9,13-*di-cis* RA (R^2=0.9998) and 0.050–32.900 pmol g^{-1} for 9-*cis* RA (R^2=0.9990). The present method can be useful for retinoic acid monitoring in clinical studies.

1. Introduction

Retinoic acid (RA) is the bioactive metabolite of vitamin A (retinol), which acts in the *all-trans*, the 13-*cis*, the 9-*cis* and the 9,13-*di-cis* isomer forms – each with unique function [1–3] (Fig. 1). In vertebrates and their embryos developing under unusual amounts of RA conditions, a wide range of abnormalities have been described; including defects of the central nervous system, eye, face, dentition, ear, limb, urogenital system, lungs, heart and aortic arch defects [4–13]. Based on the previous studies, present of RA isomers in many tissues and plasma confirms the RA critical role in vertebrates [14–26].

To investigate the RA function, homeostasis, and understanding its relationship to disease risk, RA isomers quantitative analysis is an essential requirement. Previously, analytical limitations avoided the direct RA quantification. The RA isomers are isobaric and have overlapping ultraviolet (UV) spectral profiles. Therefore, mass detection and/or single wavelength UV detection cannot distinguish the identities of geometric isomers that co-elute. Accordingly, RA isomers analysis requires the chromatographic separation of endogenous isomers before detection [27]. A series of RA isomers determination methods have been described [14,15,18,19,21]. Sensitivity and specificity of analytical measurements must be adequate to quantify endogenous RA in a physiological matrix. Different RA and other retinoid derivatives detection methods were described in the literature; including liquid chromatography–tandem mass spectrometry (LC–MS/MS), LC–MS and gas chromatography–mass spectrometry (GC–MS) [14–17,28,29]. Although these methods are sensitive, they are costly and not accessible as routinely used tools in every lab. High performance liquid chromatography–ultraviolet spectrometry (HPLC–UV) as the another determination method of retinoid derivatives has been used in previous studies [18,19]. Besides, the utility of primary detection or secondary confirmation using full UV spectrum collected by a photodiode array detector has some limitation in physiological samples treatment. Therefore, it will worth to develop an effective clean-up procedure to preconcentrate trace amount of RA in physiological samples prior to HPLC/UV.

Recently, the enrichment methods based on nanoparticles have been developed [30,31]. Quantum dots (QDs) or colloidal semiconductor nanocrystals as an important kind of nanoparticles gained increasing interest during the past decade due to their unique and novel properties. Their size-tunable optical property, broad absorption, narrow emission, intense brightness, and good photostability have made them more attractive than conventional organic fluorophores for developing analytical and biomedical applications [32–34]. QDs have a high surface reactivity, which allows strong chemisorption of a large range of compounds from different samples. But, application of these small size nanoparticles in sorption processes could be limited since of coacervation and loss of activity. Furthermore, these nanometer (nm) sized

* Corresponding author. Tel.: +98 2161112481.
E-mail address: shemiran@khayam.ut.ac.ir (F. Shemirani).

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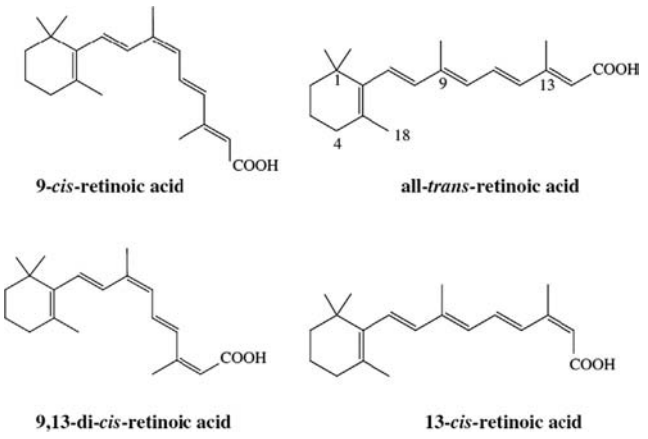

Fig. 1. Structures of endogenous RA isomers.

particles are not selective enough. These problems can be eliminated by physical or chemical modifications of the sorbent surface with specific functional groups. Recent advances in QDs nanotechnology have introduced these nanomaterials as versatile platforms for design and engineering of nanoparticle-based drug delivery vehicles [35–38]. Various internal and external triggers, such as pH, specific enzymes, temperature, ultrasound, magnetic field and light are being actively explored. Light is especially attractive, as it can be remotely applied with extremely high spatial and temporal precision. Additionally, a broad range of parameters (wavelength, light intensity, duration of exposure, and beam diameter) can be adjusted to modulate release profiles. Radiation in the UV, visible, and near infrared (NIR) regions can be applied in drug release. NIR (700–950 nm) is preferable to other types of wavelength for triggering release of drug in biological systems, because it cannot cause photoisomerization and so the geometric isomers of drug with different functions remain in virginal isomeric forms and enable us to measure their accurate concentration.

A recent study has investigated the external regulation of drug release by using NIR absorbing CdSe QD [39]. With surface modification appropriate functional groups, CdSe QDs can conjugate to proposed drugs such as RA isomers. The resulted drug loaded QDs irradiation by NIR, cause to beam energy absorption and warming [40]. By increasing the NIR intensity, the thermal and mechanical stresses are enhanced within the system and thus, the release ratio of drug increases [41]. Consequently, analyte absorption on functional groups assisted QDs can be assumed as a preconcentration method prior to quickly release of target molecules by intensive NIR beam irradiation. As far as we know, there is no report on the measurement of RA in rat whole rudimentary embryo culture (RWEC). Also, utilizing NIRQDs for direct preconcentration of analytes is a novel usage of QDs. In this study, for the first time, it was developed a new approach to preconcentration of RA in RWEC via conjugation to a QD and quick release by NIR intensive irradiation before high sensitive measurement of endogenous geometric isomers of RA by reversed phase HPLC/UV.

2. Experimental

2.1. Materials and animals

All reagents were used without further purifications. HPLC grade methanol, dichloromethane, ethylene glycol and sodium hydroxide (NaOH) were purchased from Merck Inc. (Darmstadt, Germany). Polysucrose 400 (Ficoll), Poly(D, L-lactide-*co*-glycolide) (PLGA) (Mw110,000 g mol^{-1}), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), sulfonated N-hydroxysuccinimide (sulfo-NHS), Poly(ε-caprolactone) (PCL) (Mw 110,000 g mol^{-1}), poly(vinyl alcohol) (PVA), phenylenediamine (PDA), phosphate buffered saline (PBS) and retinoic acid isomers were purchased from Sigma-Aldrich (USA). Carboxylated QDs were obtained from Evident Technologies (Troy, NY, USA). QDs used for the separation purposes were red CdSe with a primary excitation of 690 nm. Deionized water was purified with a Milli-Q system (Millipore, USA). HsdCpb: WU rats, supplied by Pasteur Institute of Iran) Tehran, Iran), were housed in the animal facility in a climate controlled room with a 12-h on/off light cycle. After 2 weeks of acclimatization, nulliparous female rats were housed together with adult male rats from the same strain and supplier for a 3-h period (9.00 am–12.00 pm). After coitus (termed as gestation day 0) females were housed singly. Water tap and standard diets were provided ad libitum. Animals were monitored daily for general health.

2.2. Apparatus

A Cecil 8453 high performance liquid chromatography with C18 Allure column (50 × 3.2 mm i.d., 5 μm particle size, Restek, Bellefonte, PA, USA) with a C18 guard column (4 × 3.0 mm i.d., Phenomenex, Torrance, CA, USA) at 350 nm UV absorbance and 1 mL/min flow rate with methanol/glacial acetic acid 1% (85:15 v/v) were used for separation of RA isomers. The fluorescence measurements were performed with F-2500 fluorospectro-photometer (Hitachi, Japan). NIR irradiations were achieved using an AM1.5G solar simulator (ABET technologies, sun 3000). Rat embryo dissections were performed with a Nikon SMZ-10 A dissection microscope equipped with a Volpi (Auburn, NY, USA) NCL 150 light source with a yellow filter. RWEC homogenizing was done using ground glass homogenizers (Duall size 21, Kontes) with PRO400DSEL Homogenizer (Bioworld, OH, USA). Evaporation in reduced pressure was performed by Rotary Evapo-Mix, Buchler Instruments (Fort Lee, NJ, USA). All scanning electron microscopy (SEM) images were obtained by Hitachi, S-2600 N scanning electron microscope (Hitachi, Japan)

2.3. Sample preparation

Rat embryos were explanted from the uterus at gestation day 7 under yellow light, with the yolk sac and ectoplacental cone left intact. A solution of phosphate buffered saline containing 30% ethylene glycol and 30% ficoll was prepared and each embryo was submerged to it in a plastic vial. This solution did not crystallize during the cooling and kept embryos in cryopreservation mode [42]. Embryos in vials, was frozen in liquid nitrogen immediately and was kept frozen at −80 °C until assay within 3 days of harvest. In assay time, frozen tissues were homogenized on ice and after EDC activation, applied to analyzing RA. The mechanism of EDC activation will be described in Section 3.1.

2.4. Modification

Stock solutions of *all-trans*, 13-*cis*, 9-*cis* and 9,13-*di-cis* RA were prepared separately by dissolving each isomer (100 μg) in methanol (100 mL) and diluted appropriately to provide stock standard solution. To EDC activation of RA, 10 mg EDC and 2 mg sulfo-NHS were added to 5 mL standard solutions under gentle stirring for 10 min at room temperature. Since RA isomers are much more stable under yellow light than under natural light conditions [43], all handlings of standard solutions and RWEC samples were done carefully in dark rooms under dim yellow light, and amber containers were used whenever possible to prevent photoisomerization and photodegradation [44]. The pH of all standards and samples was adjusted to 9.0 by adding of 1 M Tris buffer solution.

2.5. Procedure

In order to conjugate formation, 5 mL of the 150 mg L^{-1} carboxylated QDs aqueous solution was added to 5 mL of 0.1–100 pmol g^{-1} EDC activated RA solution under vortexing. Then, 5 mg PDA was subjoined to this mixture under stirring for 10 min at room temperature. It is necessary to encapsulate QD–PDA–RA conjugation before irradiation step, in order to avoid the release of RA from conjugation. Microencapsulation of QD–PDA–RA was performed by emulsifying the obtained mixture in 8 mL solution of 100 mg PLGA and 100 mg PCL in dichloromethane. The solution was emulsified by vortexing for 5 min at room temperature. By centrifuging and decantation, microcapsules part from the remnant mixture. The microcapsules were washed several times with deionized water. The morphology of microspheres was examined by SEM (Fig.2).

CdSe QDs have intensive fluorescence due to the high emission quantum yield. Analytes can affect the fluorescence of QDs via electrostatic interactions, hydrogen bonds, Van der Waals interactions, hydrophobic and steric contacts within the binding site and so on. Fig. 3 shows the fluorescence spectra of the CdSe QDs before and after conjugation to RA. The fluorescence intensity of the system was clearly decreased in presence of the analyte. Such a decrease in intensity is called fluorescence quenching. This static quenching refers to fluorophore–quencher conjugation.

In order to release RA, the microcapsules containing QD–PDA–RA conjugates were subjected to NIR radiation. Then, in order to quenching EDC activation reaction and preventing from re-conjugation of RA–QD, the samples were cooled to 4 °C, centrifuged at 1500 rpm for 3 min and filtered (0.2 μm pore size) to remove any microcapsules.

After evaporation of the obtained solution under reduced pressure, the residue was redissolved in 0.2 mL of methanol and then, 10 μL of it applied to the HPLC. For the recovery studies, the peak area of any RA isomer was determined and plotted versus the concentration of RA.

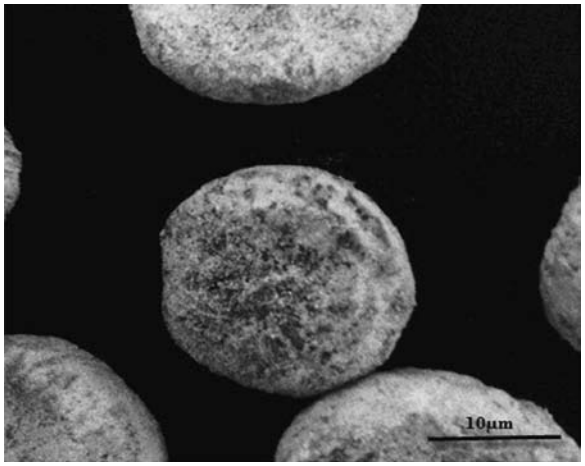

Fig. 2. SEM image of conjugated RA–QD microcapsules.

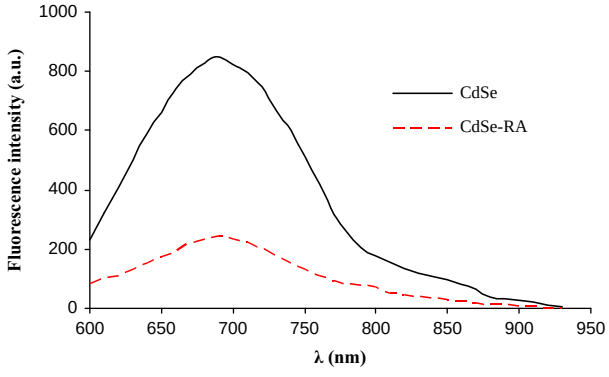

Fig. 3. Fluorescence spectra of CdSe QDs before and after conjugation to *all-trans* RA. Quenching effect of RA on QD fluorescence is tangible.

3. Results and discussion

3.1. Conjugation mechanism

The chemistry of CdSe surface has been extensively investigated. One of its outstanding properties is possessing unsaturated atoms on the surface that can react with other atoms leading to a high sorption capacity [45].With the nm size, CdSe QDs have strong potential to chemisorption. Surface modification of QDs by carboxylic groups is performed in order to prevent conglomeration and to increase their selectivity towards analyte. Sulfo-NHS is used to prepare amine-reactive esters of carboxylate groups for chemical labeling, crosslinking and solid-phase immobilization applications. Carboxylates (–COOH) can reacted to Sulfo-NHS in the presence of a carbodiimide such as EDC, resulting in a semi-stable Sulfo-NHS ester, which may then be reacted with primary amines ($–NH_2$) to form amide crosslinks. Although Sulfo-NHS is not required for carbodiimide reactions, its use greatly enhances coupling efficiency. Furthermore, using Sulfo-NHS makes it possible to perform a two-step reaction. Therefore, PDA can bind to both EDC activated RA and QD through two its NH_2 groups. Fig. 4 shows the schematic view of conjugation process of RA to CdSe QDs.

3.1.1. Study of the concentration of QD

To achieve the most effective amount of QDs, the concentration of CdSe QDs as sorbent was ranged from 20 to 200 mg L^{-1}. As it can be seen in Fig. 5, all isomers of RA have similar extraction efficiency growth with the increase of QDs concentration up to 80 mg L^{-1}, and then remained constant. Because of some other compounds that could be present in physiological samples and probably conjugate with QDs, a concentration of 120 mg L^{-1} was used in experiments.

3.2. Release mechanism

Between multifarious triggers, light is the most appropriate agent for the release of RA isomers from the conjugation, because of controllable process of exerting. The use of NIR beams for provocation of QDs allows us to release RA in physiological samples with no change in isomer forms. However, very few organic chromophores absorb in this region, and even fewer are capable of converting the absorbed energy into a chemical or thermal response that can be used to trigger analyte release. Some metal nanoparticles emerged as useful agents for photothermal therapy after they were shown to have strong absorption in the NIR region (four–five times higher than conventional photo-absorbing dyes [46]) and tunable optical resonances. CdSe QDs have intensive absorption in the NIR region, too. These QDs absorb light efficiently due to coherent oscillations of metal conduction band electrons in strong resonance with visible and infrared frequencies of light. Photo excitation of metal nano structures results in the formation of a heated electron gas that cools rapidly within 1 ps by exchanging energy with the nanoparticle lattice. The nanoparticle lattice, in turn, rapidly exchanges energy with the surrounding medium on the timescale of 100 ps, causing localized heating [47]. Spontaneous local heating to temperatures well above hundreds of °C [48,49] induces significant thermal and mechanical stress within the

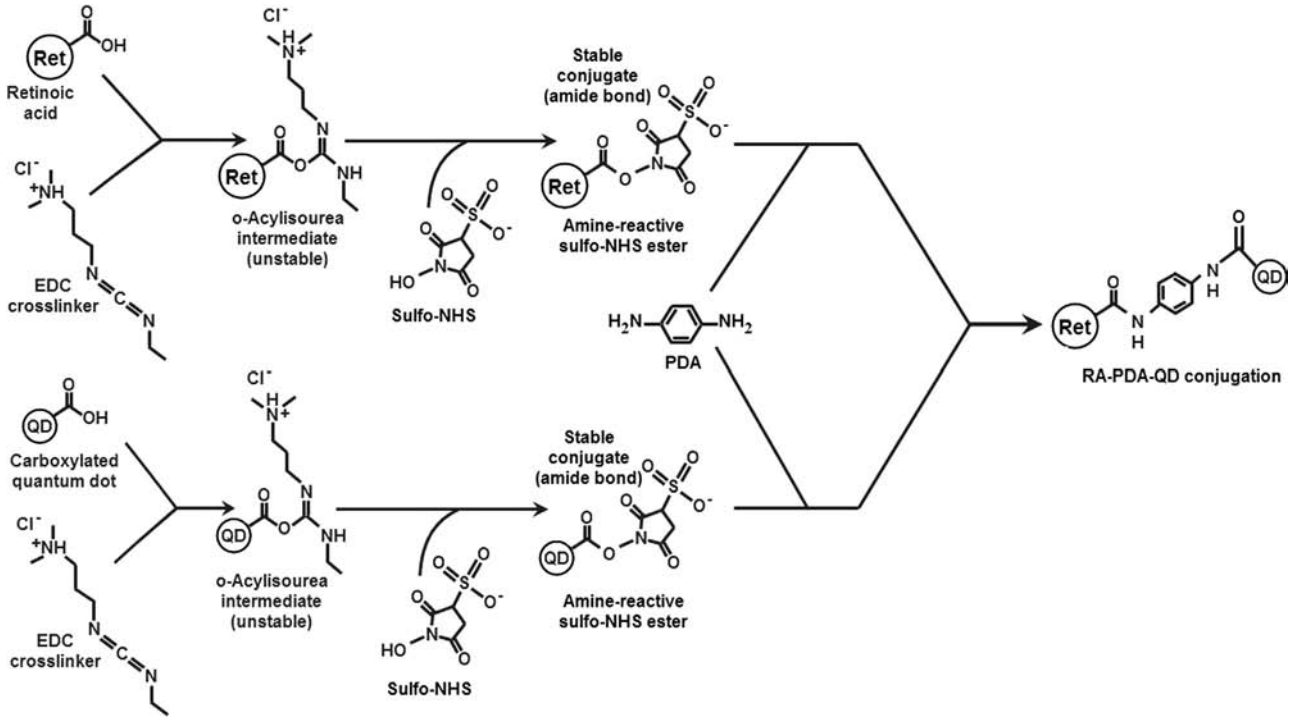

Fig. 4. Schematic conjugation of RA–PDA–QD. Addition of Sulfo-NHS to EDC crossliking reactions, increases efficiency and enables retinoic acid to be activated for storage and later use.

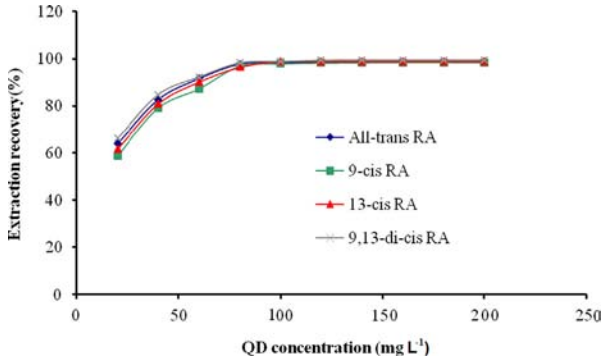

Fig. 5. Effect of QDs concentration on RA recovery. The NIR Irradiance intensity was kept in 150 mW/cm^2 at 15 min.

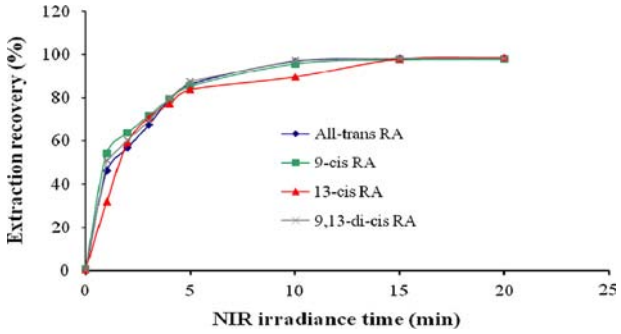

Fig. 6. Effect of NIR Irradiance time on RA recovery. QDs concentration in this experiment was adjusted in 120 mg L^{-1} and the NIR Irradiance intensity were kept in 150 mW/cm^2.

system and thus causes rupture of the conjugation and subsequent rapid release.

3.2.1. *Effect of exposure duration*

The effect of NIR irradiation time was examined in the range of 1–20 min with the constant irradiation intensity. As shown in Fig. 6, by increasing the irradiation time from 1 to 15 min, the recovery of all RA isomers was improved and after 15 min, the increase in recovery was not significant. So, duration of exposure was adjusted to 15 min for experiments.

3.2.2. *Effect of NIR irradiation intensity*

The influence of NIR irradiation intensity on the release of RA was studied at the range between 50 and 600 mW/cm^2. The results were shown in Fig. 7. As could be seen, the RA release at intensity less than 130 mW/cm^2, is too slow. Nonetheless, NIR irradiancy more than 130 mW/cm^2 can cause a quick release. The RA release rate did not change appreciably at more than 350 mW/cm^2.

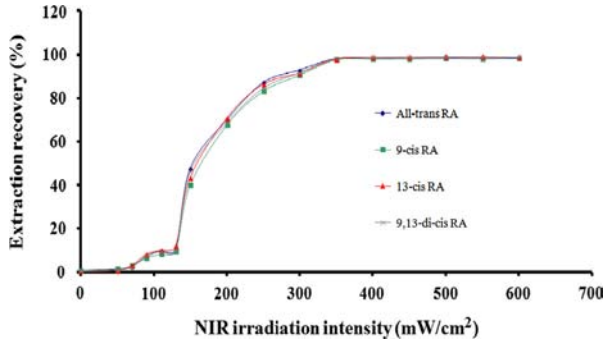

Fig. 7. Effect of NIR Irradiance intensity on RA recovery. QDs concentration in this experiment was adjusted in 120 mg L^{-1} and the NIR radiation time were kept at 15 min.

3.3. *Analytical figures of merit*

Investigation of practical applicability was performed using the external standard method for calibration and several analytical

Table 1
Comparison of the published methods for retinoic acid determination with the proposed method.

Method	Matrix	Analyte	Linear range	R^2	RSD range, %	LOD	LOQ	Ref.
SPE-HPLC	Human serum	13-*cis* RA	–	0.9997	–	0.04[a]	0.09[a]	50
SPE-HPLC	Human serum	*All-trans* RA	–	0.9995	–	0.06[a]	0.12[a]	50
UV–DAD	Galenicals	13-*cis* RA	0.32–6.4[b]	0.9999	–	12[c]	–	51
Fl	Galenicals	13-*cis* RA	0.15–5.9[b]	0.9999	–	7[c]	–	51
UV–DAD	Galenicals	9-*cis* RA	0.28–5.6[b]	0.9997	–	11[c]	–	51
Fl	Galenicals	9-*cis* RA	0.20–5.0[b]	0.9993	–	7[c]	–	51
UV–DAD	Galenicals	*All-trans* RA	1.1–28[b]	0.9999	–	11[c]	–	51
Fl	Galenicals	*All-trans* RA	1.1–28[b]	1.0000	–	5[c]	–	51
MEKC	Rabbit serum	*All-trans* RA	0.029–2.2[b]	0.9960	2.1–2.7[e]	0.026[b]	0.36[b]	52
MEKC	Rabbit serum	13-*cis* RA	0.033–2.5[b]	0.9920	2.4–3.3[e]	0.030[b]	0.49[b]	52
LC/MS/MS	Mouse pancreas	9-*cis* RA	–	–	–	<0.05	–	53
HPLC/MS/MS	Seawater	*All-trans* RA	–	–	–	0.02[f]	–	54
HPLC/MS/MS	Seawater	13-*cis* RA	–	–	–	0.03[f]	–	54
HPLC/MS/MS	Seawater	9-*cis* RA	–	–	–	0.04[f]	–	54
HPLC/MS	Rat testis	Retinoic acid	2–80[g]	$r>0.99$	–	0.17[c]	0.53[c]	55
UPLC/MS/MS	Natural cyanobacteria (intracellular)	*All-trans* RA	–	–	–	–	0.3[f]	56
UPLC/MS/MS	Natural cyanobacteria (intracellular)	13-*cis* RA	–	–	–	–	0.3[f]	56
UPLC/MS/MS	Natural cyanobacteria (intracellular)	9-*cis* RA	–	–	–	–	0.8[f]	56
QD-HPLC	RWEC	*All-trans* RA	0.040–34.600	0.9996	0.6–1.1	0.0230[d]	0.0992[d]	This study
QD-HPLC	RWEC	13-*cis* RA	0.070–34.200	0.9992	1.3–2.2	0.0221[d]	0.1030[d]	This study
QD-HPLC	RWEC	9,13-*di-cis* RA	0.050–32.900	0.9998	0.8–1.9	0.0206[d]	0.0998[d]	This study
QD-HPLC	RWEC	9-*cis* RA	0.050–35.300	0.9990	0.9–1.7	0.0217[d]	0.1006[d]	This study

SPE: solid-phase extraction, DAD: diode array detection, Fl: fluorimetric detection, LC: liquid chromatography, MS: mass spectrometry, MEKC: micellar electrokinetic chromatography, and UPLC: ultra performance liquid chromatography

[a] μmol L^{-1}.
[b] μg mL^{-1}.
[c] pmol.
[d] pmol g^{-1}.
[e] between assay (for a 3 days period).
[f] ng L^{-1}.
[g] ng mL^{-1}.

performance characteristics were investigated. The linear regression analysis, using peak area as the function of concentration, was constructed by analyzing series of standard solutions. Under optimized conditions, relative standard deviations (RSD) were acquired in the range of 0.6–2.2%. The method detection limit (DL) was defined as the lowest concentration of analyte in physiological matrices that could be analyzed by the described method, generating a signal with an S/N ratio of 3 after preconcentration. The obtained DL was 23.0×10^{-3} pmol g^{-1} for *all-trans* RA, 22.1×10^{-3} pmol g^{-1} for 13-*cis* RA, 21.7×10^{-3} pmol g^{-1} for 9-*cis* RA and 20.6×10^{-3} pmol g^{-1} for 9,13-*di-cis* RA. Table 1 compares the characteristic data of our method with those reported in literature.

3.4. Application to RWEC

0.3 g of homogenized RWEC sample was prepared according to the described method in sample preparation section. In order to achieve QD–PDA–RA conjugation, 1 mg EDC, 0.2 mg Sulfo-NHS and 0.5 mL of carboxylated QDs aqueous solution (100 mg L^{-1}) was added to sample. Then, 0.5 mg PDA was subjoined to the mixture under vortexing. After microencapsulation of QD–PDA–RA, the RA was insulated from microcapsules under NIR beams and the sample then, was cooled to 4 °C, centrifuged at 1500 rpm for 3 min and filtered to remove any microcapsules. The residual solution below the filter was evaporated under reduced pressure and total RA isomers were redissolved in 0.2 mL of methanol and then, 10 μL of it applied to the HPLC. As kithed in Fig. 8, notwithstanding the observation of *all-trans*, 9-*cis* and 9,13-*di-cis* RA peaks in resulted chromatogram, 13-*cis* RA was not found in RWEC. Explained method was used for eight RWEC individual samples and the acquired mean concentration is 3.2, 11.7 and 5.3 pmol g^{-1} for 9,13-*di-cis*, *all-trans* and 9-*cis* RA, respectively.

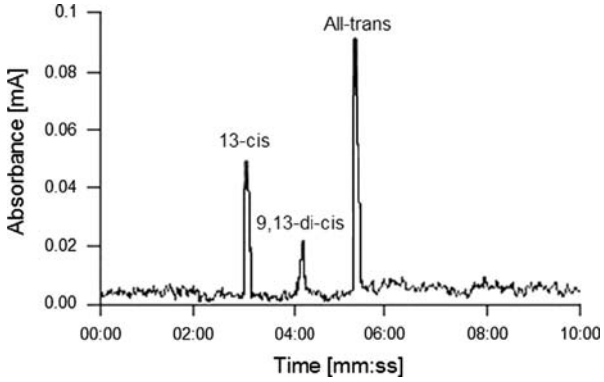

Fig. 8. Reversed-phase HPLC chromatogram of obtained RA from RRET after described preconcentration method. The isocratic elution was performed with 1% acetic acid and methanol (15/85, v/v) by UV/vis detector at 350 nm.

In order to validate the method, spiking the real samples was carried out (standard addition technique). The recovery of the added standards was calculated after applying the proposed method. Good correlation was achieved between the added and measured amounts. Generally, the recoveries of RA isomers were obtained in the range of between 94.2 and 98.7%. The results were listed in Table 2.

4. Conclusion

In the current study, a novel sensitive method was developed for preconcentration and quantitative measurement of trace amount of retinoic acid by surface modified CdSe quantum dots. The method was then used to investigate retinoic acid geometric isomers concentration in one-week embryonic tissue of rat. Three

Table 2
Recoveries of retinoic acid isomers from rat whole rudimentary embryo culture.

Analyte	Spiked (pmol g^{-1})	Found (pmol g^{-1})[a]	Recovery (%)
All-trans retinoic acid	0	0.0610 ± 0.0091	–
	0.1	0.1583 ± 0.0065	97.3
	1	1.0220 ± 0.0103	96.1
	10	9.6961 ± 0.1307	96.3
13-*cis* retinoic acid	0	ND	–
	0.1	0.0980 ± 0.0088	98.0
	1	0.9764 ± 0.0141	97.6
	10	9.5617 ± 0.1201	95.6
9,13-*di-cis* retinoic acid	0	0.0521 ± 0.0069	–
	0.1	0.1463 ± 0.0072	94.2
	1	1.0254 ± 0.0190	97.3
	10	9.7000 ± 0.2117	96.4
9-*cis* retinoic acid	0	ND	–
	0.1	0.0966 ± 0.0091	96.6
	1	0.9870 ± 0.0168	98.7
	10	9.4986 ± 0.2621	94.9

ND: not detected.

[a] Mean $\pm$ SD, ($n=8$)

RA isomers were detected in RWEC with the concentrations between 3.2 and 11.7 pmol g^{-1} and 9-*cis* RA was not found at the sensitivity of the described method. The more important aspect of this study is the usage of surface modified quantum dots as a preconcentration agent for organic compounds in biological matrices. This method gives good accuracy, low limit of detection and excellent precision for the target analytes due to conjugation of RA–QD and release by near infrared (NIR), which shows its potentiality in trace analysis of RA in physiological samples with complex matrixes.

Acknowledgments

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