

## Investigation of stability and activity of quaternized zinc phthalocyanine photosensitizer with fused extended conjugation in vitro conditions

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### ABSTRACT

Quaternized zinc phthalocyanine (QZnPc) which is water soluble is a promising candidate for photodynamic therapy (PDT) applications. The physicochemical properties like the stability, activity, particle size, surface charge of tetrakis-(4-[(1E)-3-iminoprop-1-en-1-yl]-N,N,N-trimethylphenylammonium) phthalocyaninato zinc(II) tetraiodide (II) quaternized zinc phthalocyanine (fused extended conjugation, QZnPc-FE) were investigated. The Zeta Potential Analyzer was used for this purpose. QZnPc-FE is freshly synthesized, water soluble quaternized zinc phthalocyanine and used as potential photosensitizer for PDT application. The stability and activity behavior of QZnPc-FE was determined in vitro conditions such as different pHs and in simulated body fluids as function of time via Zetasizer measurements and UV/VIS absorbances, respectively. Morphology of the QZnPc-FE was determined via XRD and the organic solvent effect with different polarity on QZnPc-FE was checked by UV/VIS. The optimum stability and activity conditions of QZnPc-FE in vitro conditions were determined, and the obtained results showed that the studied compound can be used for medical (PDT) and pharmaceutical applications.

**Keywords:** Water Soluble Quaternized Zinc phthalocyanine; Zeta Potential; Particle Size; Stability; Particle Charge; Activity

### INTRODUCTION

Phthalocyanines (Pcs) containing 18  $\pi$ -electron system include both aromatic and synthetic tetrapyrrolic systems. Recently, phthalocyanines and metallo phthalocyanines (MPcs) have been applied in lots of researchs such as, liquid crystals, chemical sensors, semiconductors, non-linear optics catalysis and especially last years at biomedical applications as photodynamic therapy (PDT). Zinc phthalocyanine derivatives (ZnPcs) have been investigated because of electronic configuration of the central  $Zn^{2+}$  ion; they cause optical spectra that are not complicated by additional bands, as in partially filled transition-metal Pc complexes. They are also used in PDT owing to their strong absorption of visible radiation between 600 and 850 nm, which offers high penetration of tissue and which is capable of photosensitization of singlet oxygen. In PDT applications, photosensitizer drugs are injected into the patient's blood stream and because the blood itself is a hydrophilic system, water solubility becomes crucial for a potential photosensitizer in PDT [1-3].

The ZnPcs complex used in this study has continual conjugation bond linkages (tetrakis-(4-[(1E)-3-iminoprop-1-en-1-yl]-N,N,N-trimethylphenylammonium) phthalocyaninato zinc(II) tetraiodide (II) (fused extended conjugation, QZnPc-FE) has high singlet oxygen quantum yield [4]. Because of this, QZnPc-FE can be used as drug candidate for cancer therapy. Particle size, particle shape and surface charge of particles in vitro conditions are a key role in the cellular uptake of drug particles. The surface charge of the particles affects the attachment of particles to cell membrane [5]. Zeta potential (ZP) is a crucial parameter of particles in solution to estimate the surface charge, which can be employed for understanding the physical stability of solutions. Zeta potential parameter refers the degree of repulsion between the charged particles in the dispersion. High ZP values mean highly charged particles and thus no aggregation occurs due to electric repulsion between particles. The low ZP values refer interaction between particles and thus this overcomes repulsion between particles, and coagulation occur. The ZP value of  $-30$  mV to  $+30$  mV is considered optimum for good stabilization of a nanodispersion [6]. Zetasizer measurements have been used in many areas from paint to medical industries to control the stability [7-13].

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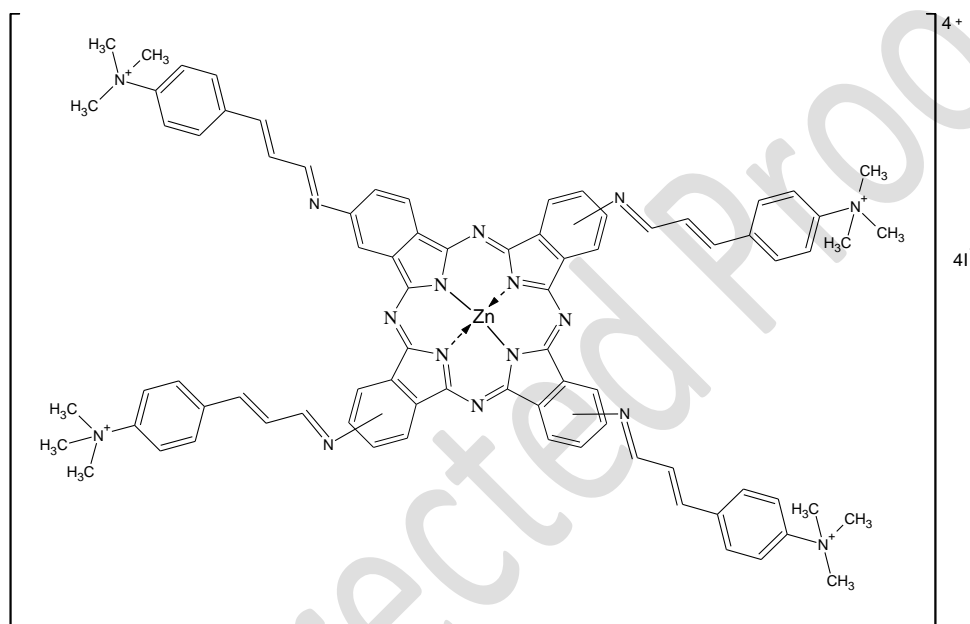
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In the present study, solution properties of QZnPc-FE in different pHs and simulated body fluids as a function of time were determined to by using zetasizer and UV/VIS measurements.

## MATERIAL AND METHODS

### MATERIALS

Quaternized zinc phthalocyanine which is called as tetrakis-(4-[(1E)-3-iminoprop-1-en-1-yl]-N,N,N-trimethylphenylammonium) phthalocyaninato zinc(II)] tetraiodide (Scheme 1) was synthesized freshly according to previous research paper [14].



**Scheme 1.** Molecular structure of tetrakis-(4-[(1E)-3-iminoprop-1-en-1-yl]-N,N,N-trimethylphenylammonium) phthalocyaninato zinc(II)] tetraiodide quaternized zinc phthalocyanine

The particle size and zeta potential of QZnPc-FE in different pHs and simulated body fluids such as %5 dextrose, % 0.9 (Isotonic) NaCl and PBS solutions were measured via Brookhaven 90 Plus/Bi-MAS (Multi Angle Particle Sizing) and Brookhaven Zeta Potential Analyzer at 37 °C. The device gives the particle size, polydispersity, mobility and zeta potential values automatically calculated by taking the average of 5 measurements and the average values were given mean  $\pm$  standard deviation. The statistical parameters as mean, variance and standard deviation of zetasizer measurement results changing with pH and time effect in simulated body fluids were calculated and added to related tables. The concentration of solutions were kept as 0.3 mg/mL.

### METHODS

The particle size measurements of samples were determined with the dynamic light scattering (DLS) and the hydrodynamic particle diameter is calculated via the Einstein-Stokes relationship (Eq.1):

$$D = \frac{kT}{6\pi\eta R_h} \quad (1)$$

where, k is Boltzmann constant, T is ambient temperature in K Kelvin,  $\eta$  is viscosity of solvent D is diffusion coefficient and  $R_h$  is the hydrodynamic diameter of the spherical particles.

The polydispersity index (PDI) is a measure for the width of the particle size distribution and it is calculated via DLS. The smaller the PDI the more homogeneous the particles are distributed in the sample.

The zeta potential of solution is determined according to Smoluchowski assumption (Eq.2) as following:[6]

$$\zeta = (\eta \cdot \mu_e) / \varepsilon \quad (2)$$

in which  $\mu_e$  is electrophoretic mobility,  $\varepsilon$  is the dielectric constant and  $\eta$  is the viscosity of solvent.

Phosphate Buffer Saline Tablets (PBS, pH=7.4) were purchased from Sigma-Aldrich, %5 dextrose (pH=4) and %0.9 NaCl solutions (pH=5.7) were taken as biological grade. The controlling activity of QZnPc-FE in different pHs and simulated body fluids such as %5 dextrose, % 0.9 Isotonic NaCl and PBS solutions were checked by Shimadzu UVmini-1240 Spectrophotometer. The organic solvent effect with different polarity such as DMF, THF, DMSO on QZnPc-FE was checked by UVmini-1240 Spectrophotometer.

The XRD pattern of the QZnPc-FE was determined via PANalytical X'Pert Pro Model Polycrystal XRD device with internal wavelengths used from anode material as Copper (Cu) and generator settings 40 mA, 45 kV. The related XRD pattern was obtained at room temperature.

## RESULTS AND DISCUSSION

### Determination of stability and activity of QZnPc-FE at different pHs and simulated body fluid solutions:

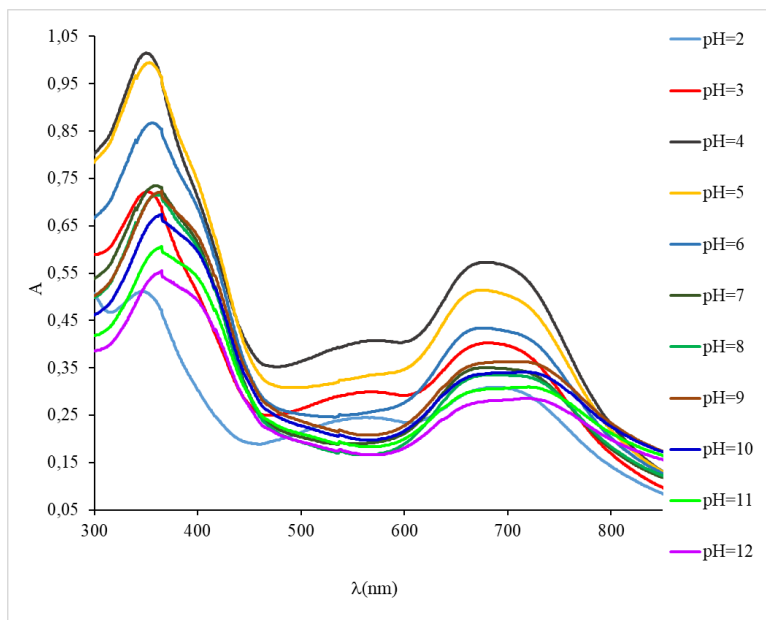
In order to investigate physical properties of QZnPc-FE in solution, dispersions prepared at different pH values, and measured with both Zetasizer and UV/VIS spectrophotometer, respectively. Zetasizer measurements such as polydispersity, particle size, mobility and zeta potential of QZnPc-FE give the stability information in aqueous solution and were done via Zetasizer in different pHs. The zetasizer measurement values of QZnPc-FE in different pHs were given Table 1.

**Table 1.** pH effect on polydispersity, particle size, mobility and zeta potential of QZnPc-FE

pH	PDI	Particle Size (nm)	Mobility (m <sup>2</sup> /V.s)	Zeta Potential (mV)
2	0.3	280±13.5	3.7	47.5±1.2
3	0.3	230±7.6	3.9	49.7±1.9
4	0.3	250±6.3	3.9	50.4±0.9
5	0.3	300±8.2	2.2	28.1±0.8
6	0.4	835±4.9	1.9	24.1±1.7
7	0.4	745±5.8	1.9	24.2±0.4
8	0.4	730±6.4	1.3	16.4±1.2
9	0.3	1850±72.4	0.6	7.4±0.6
10	0.3	2930±101.4	-0.4	-4.5±0.6
11	0.3	2830±182.8	-1.3	-17.1±0.5
12	0.3	3370±349.6	-1.7	-21.9±0.4
Mean	0.3	1300	1.5	18.6
Variance	0.0022	103346.9	3.9	654
Standart Deviation	0.047	1156	1.99	25.9

The PDI values of QZnPc-FE in studied pHs were found between 0.3 and 0.4. It means that QZnPc-FE particles in studied pHs are monodispers and show homogenous dispersion. The particle size of QZnPc-FE varied between 200 and 730 nm upto pH=8. After increasing pHs, the particles of QZnPc-FE were swelling and particle size was increasing. The QZnPc-FE particles in different pHs were positively charged upto pH=10 and preserve the stability because of higher zeta potential values as about 47 mV. After pH=10, QZnPc-FE is negatively charged. It was not seen any aggregation and coagulation of QZnPc-FE particles at different pHs. Wang et al. [15] have been reported that drugs should be negatively charged under normal physiological conditions to ensure effective blood transmission, while be positively charged in tumor tissues to obtain better cellular uptake and anticancer activity. Thus, the preparation of anticancer drugs which can switch their charge from negative to positive in response to tumor microenvironment will be very meaningful. The pH effect on zeta potentials of QZnPc-FE in different pH solutions shows that the QZnPc-FE has charge reversal sensitivity and so, QZnPc-FE is useful for PDT treatment.

The activity and also stability of QZnPc-FE in studied pHs were checked by UV/VIS spectroscopy and the spectra are presented in Fig.1.



**Figure 1.** The UV/VIS spectra of QZnPc-FE at different pHs

The characteristic absorbance spectra of QZnPc-FE shows that spectra has two bands (B and Q) and 1 shoulder which are characteristic peaks of QZnPc-FE. One in UV region which is called B- band in the range 300-350 nm and the other in visible the region (600-650 nm) which is called Q-band. The activity controlling of QZnPc-FE particles at different pHs, simulated body fluids and organic solvents was carried out by these band intensities.[14]

The Q-band absorption of QZnPc-FE were broden and shoulder was absence after pH=6. QZnPc-FE showed the max activity at pH=4 and min activity at pH=12.

The particle size and zeta potential changes of QZnPc-FE in different simulated body fluids such as 5% Dextrose, PBS and %0.9 NaCl as a function of time were determined and the results were given in Table 2, 3 and 4 respectively.

**Table 2.** Time effect on particle size, polydispersity, mobility and zeta potential of QZnPc-FE in 5% Dextrose

Time (min)	PDI	Particle Size (nm)	Mobility (m <sup>2</sup> /V.s)	Zeta potential (mV)
0	0.3	590±27.6	2.7	34.1±0.7
15	0.3	600±17.2	2.3	29.9±1.9
30	0.3	590±12.1	2.4	30.9±2.0
45	0.3	540±26	2.4	30.6±1.1
60	0.3	550±18.2	2.2	28.9±1
120	0.3	615±46.2	2.2	28.5±0.7
180	0.3	580±21.2	2.1	26.4±1.3
1440	0.3	560±24.5	1.5	19.6±1.0
2880	0.4	650±86.2	0.8	10.3±1.5
5760	0.4	1225±26.6	0.6	7.8±1.8
10080	0.2	1500±33.5	0.2	2.6±0.5
Mean	0.31	730	1.76	22.7

<b>Variance</b>	0.029	103346	0.73	119
<b>Standart Deviation</b>	0.054	322	0.86	10.9

The particles of QZnPc-FE in 5% Dextrose solution were monodispers found between 0.3 and 0.4 and showed homogenous dispersion. The particle size of QZnPc-FE particles were increasing with increasing between 540 and 1500 nm. The stability of QZnPc-FE particles in 5% dextrose was decreasing with increasing time from 34 mV to 2.6 mV at 7th days. QZnPc-FE particles in 5% dextrose were positively charged.

**Table 3.** Time effect on polydispersity, particle size, mobility and zeta potential of QZnPc-FE in PBS

<b>Time (min)</b>	<b>PDI</b>	<b>Particle size (nm)</b>	<b>Mobility (m<sup>2</sup>/V.s)</b>	<b>Zeta Potential (mV)</b>
<b>0</b>	0.2	1490±97.5	0.3	3.6±1.0
<b>15</b>	0.1	2535±53.8	0.3	4.4±4.2
<b>30</b>	0.2	2620±140.5	0.3	6.9±1.3
<b>45</b>	0.1	3100±123.0	-0.3	-4.5±1.7
<b>60</b>	0.2	3725±194.9	-0.4	-4.7±2.2
<b>120</b>	0.2	3730±164.8	-0.4	-5.8±2.2
<b>180</b>	0.2	2775±91.3	-0.5	-6.4±1.8
<b>1440</b>	0.2	3310±231.7	-0.6	-7.9±1.3
<b>2880</b>	0.2	5465±610.7	-1.1	-13.9±1.5
<b>5760</b>	0.2	3410±178.5	-1.0	-12.8±1.3
<b>10080</b>	0.1	3915±241.3	-1.1	-14.8±0.5
<b>Mean</b>	0.17	3280	-0.41	-5.08
<b>Variance</b>	0.0022	1007792	0.29	55.13
<b>Standart Deviation</b>	0.047	1003.9	0.54	7.42

The particles of QZnPc-FE in PBS solution were monodispers found between 0.1 and 0.2 and QZnPc-FE particles in PBS are also monodipers. The particle size of QZnPc-FE particles were slightly increasing between 1500 and 5500 nm with increasing time. The stability of QZnPc-FE particles in PBS was decreasing with increasing time from 3 mV to -14.8 mV at 7th days. The charge of QZnPc-FE particles in PBS was positive up to 30 min, after 30 min the QZnPc-FE particles in PBS were negatively charge.

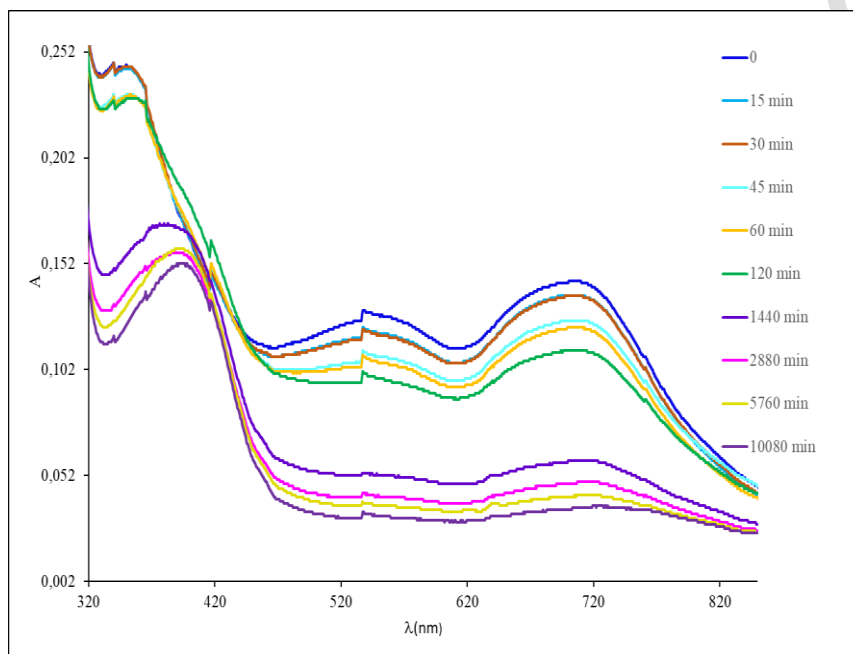
**Table 4** Time effect on polydispersity, particle size, mobility and zeta potential of QZnPc-FE in isotonic NaCl

<b>Time (min)</b>	<b>PDI</b>	<b>Particle size (nm)</b>	<b>Mobility</b>	<b>Zeta Potential (mV)</b>
<b>0</b>	0.2	2965±75.3	1.3	16.7±3.1
<b>15</b>	0.2	3000±203.7	0.9	12.7±2.5
<b>30</b>	0.2	3690±60.8	0.3	3.9±2.5
<b>45</b>	0.2	3245±95.8	0.4	5.3±0.9
<b>60</b>	0.2	3745±150.4	0.8	10.3±1.7
<b>120</b>	0.2	3380±143.7	0.7	9.4±2.1
<b>180</b>	0.2	3200±90.6	0.6	7.9±1.1
<b>1440</b>	0.2	3205±285	0.6	7.8±0.9

<b>2880</b>	0.2	3110±206.1	0.2	2.6±1.2
<b>5760</b>	0.2	3530±159.6	0.1	1.1±0.6
<b>10080</b>	0.2	3605±160.5	0.2	2.6±1.5
<b>Mean</b>	0.2	3245	0.6	6.78
<b>Variance</b>	2.93	75004	0.13	22.47
<b>Standart Deviation</b>	8.56	273.87	0.36	4.74

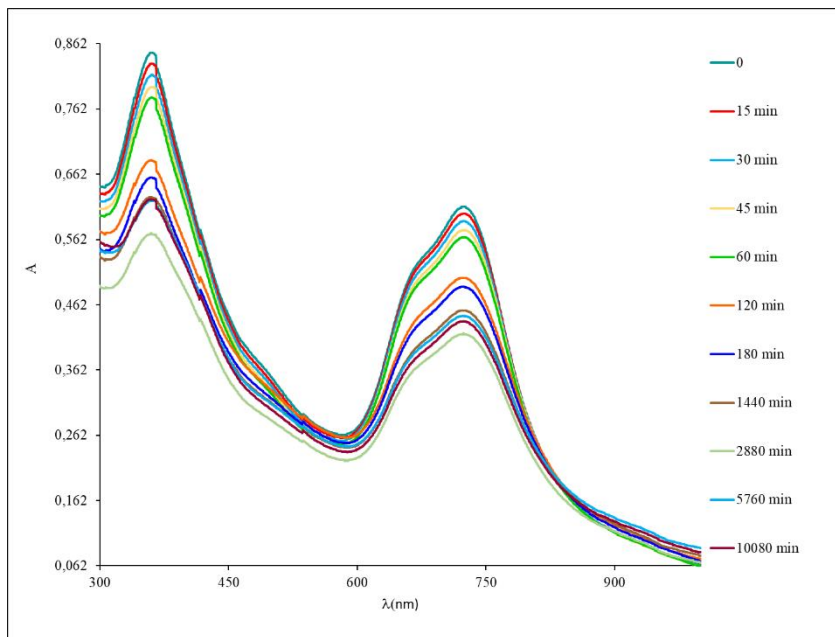
The particles of QZnPc-FE in isotonic NaCl solution were monodispers found as 0.2 and QZnPc-FE particles in isotonic NaCl are also monodipers. The particle size and charge of QZnPc-FE particles did not change in isotonic NaCl with increasing time. The charge of QZnPc-FE particles in isotonic NaCl was positively charged.

The activity and stability of QZnPc-FE in % 5 dextrose, PBS and isotonic NaCl were checked by UV/VIS spectroscopy and the spectra were given in Fig.2,3 and 4, respectively.



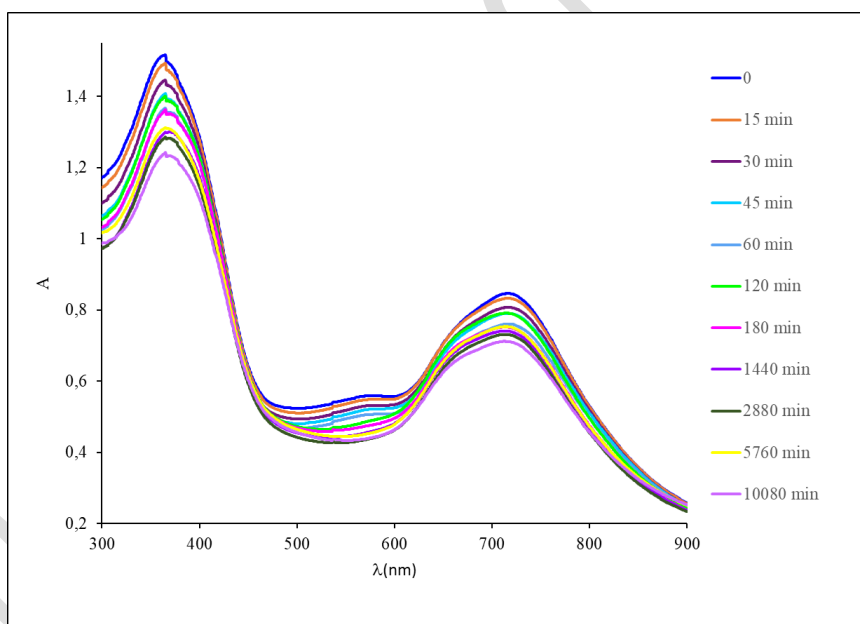
**Figure 2.** The UV/VIS spectra of QZnPc-FE in % 5 dextrose

The activity of QZnPc-FE in %5 dextrose decreased sharply after 120 min and soret (B) bands shifted from 360 nm to 400 nm (bathochromic shift) whereas the Q bands were broden with time.



**Figure 3.** The UV/VIS spectra of QZnPc-FE in PBS solution

The activity of QZnPc-FE decreased sharply after 60 min and Soret (B) and Q-bands did not change with time.

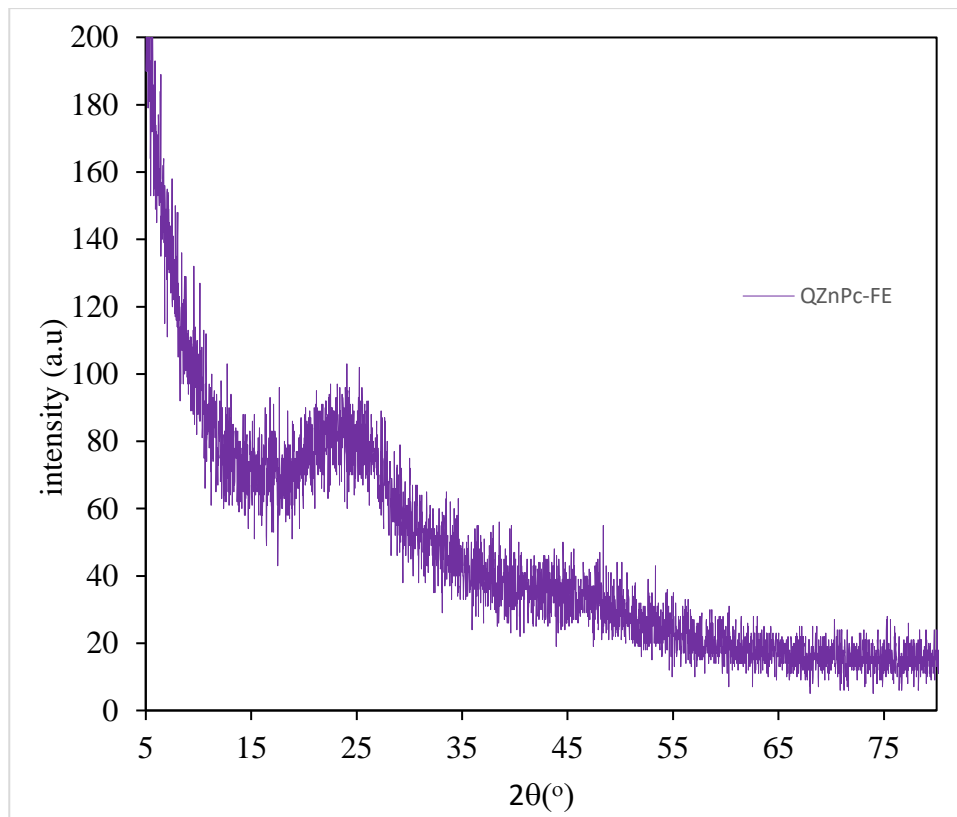


**Figure 4.** The UV/VIS spectra of QZnPc-FE in isotonic NaCl solution

The activity of QZnPc-FE in isotonic NaCl solution gradually decreased with time and Soret (B) and Q-band absorptions did not change with time. It was not seen any aggregation and QZnPc-FE preserve the stability in studied solutions.

### XRD Characterization and Different Organic Solvent Effect on QZnPc-FE

Morphological characterization of QZnPc-FE was done by XRD and the XRD pattern of QZnPc-FE was given in Fig.5.

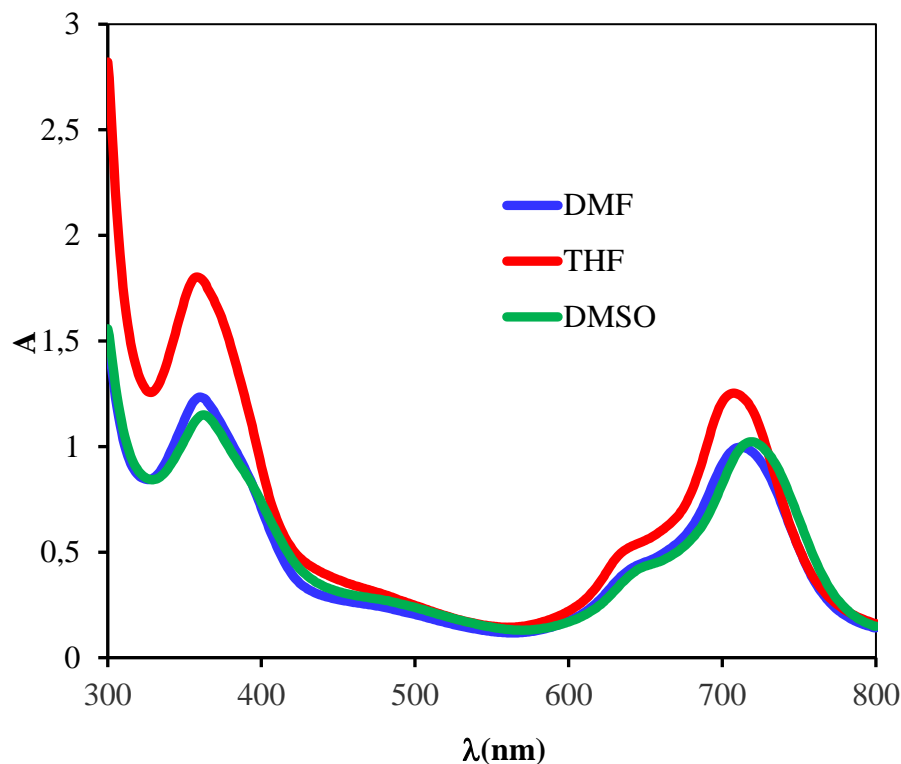


**Figure 5.** The XRD pattern of QZnPc-FE

The main broad and hump peak at  $2\theta=23^\circ$  can be corresponding to be related to amorphous nature of QZnPc-FE. [16]

The organic solvent effects such as THF (relative polarity=0,207), DMF(rp=0,386), and DMSO(rp=0,444) [17] on QZnPc-FE were determined via UV/VIS technique and the spectra were given in Fig.6.





**Figure 6.** The UV/VIS Spectra of QZnPc-FE in THF, DMF, and DMSO (increasing polarity)

The absorbance spectra of QZnPc-FE in THF, DMF, and DMSO solvents showed that both of 3 spectra have two band and 1 shoulder which are characteristic peaks of QZnPc-FE. The characteristic B band of QZnPc-FE was observed at the same wavelength as 360 nm. It showed that the absorbance increase strongly with decreasing polarity of solvent, and no changes occur in flat area in range (400-600nm). The absorbance for Soret and Q-bands of QZnPc-FE in DMF and DMSO decreased strongly with polarity of solvent. The absorption spectra showed that the maximum absorption peak shifts towards the longer wavelength with increase the polarity of solvent. and while the characteristic Q band of QZnPc-FE in THF were observed in 700, the characteristic Q bands of QZnPc-FE in DMSO and DMF solvent were shifted and shown at 720 nm [18].

## CONCLUSION:

The stability and activity of QZnPc-FE in vitro conditions were investigated by zetasizer measurements and absorbance spectrums. XRD diffraction pattern of QZnPc-FE revealed that the QZnPc-FE was amorphous in nature.

The greatest absorbance is stated to be two spectrum absorption bands, one in the UV and the other in the visible region and we used this information to determine the activity of QZnPc-FE in vitro conditions. The QZnPc-FE particles in solutions were determined as monodisperse because of PDI between 0.1 and 0.3. QZnPc-FE was positively charged at the pHs 2-9 while it was negatively charged at pHs 10-12. QZnPc-FE particles in dextrose and isotonic NaCl solutions were positively charged in studied time whereas QZnPc-FE particles in PBS were positively charged upto 30 min after that negatively charged and the Q-band absorptions broaden. QZnPc-FE particles preserved the stability in vitro conditions and it was not seen any aggregation, coagulation and color changes in vitro conditions. The charge reversibility of QZnPc-FE at different pHs and in vitro environments is promising for its use as a cancer treatment drug.

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