Supplementary information

S1. Materials and Methods

S1.1 Structural characterization of BQCA-SA LDC

S1.1.1 NMR Spectroscopy

The analytical techniques like ^{1}H NMR (Proton NMR) and ^{13}C NMR (Carbon NMR) was performed using the solvent Deuterated chloroform ($CDCl_3$) at an instrumental frequency of 300 MHz or 400 MHz or 500 MHz to confirm the chemical structural configuration of the prepared conjugate. The Hz (Hertz) is taken as a unit for coupling constant, depicted by J. The chemical shift denoted by δ and the units present on the scale were in (parts per million) ppm, downfield from the internal standard TMS (trimethyl silane, δ = 0.0) and the signalling peaks were showed as follows: Singlet-s, Doublet-d, Doublet of doublet-dd, doublet of triplet-dt, triplet-t, quartet-q, a quartet of doublet-qd, multiplet-m, broad-br, a triplet of triplet-tt.

S1.1.2 Fourier Transform Infra-Red (FTIR) Spectra

The FTIR analysis of the conjugated product was performed using the KBr pelletization technique. Scanning of the pellet (Conjugate+KBr) was performed at IR range 4000–400 cm^{-1} using the FTIR spectrophotometer (Shimadzu, Japan).

S1.1.3 Mass Spectroscopy

To determine the mass of the synthesized LDC, high-resolution mass spectra (HRMS) were recorded on a Waters-TOF spectrometer.

S 1.2 Lyophilization of optimized BQCA-SA-P80-NPs

The optimized batch of BQCA-SA-P80-NPs was freeze-dried to enable long term stability. *Briefly,* optimized BQCA-SA-P80-NPs suspension (5 ml) was take in 6R vials. Cryoprotectant (mannitol) was added to the suspension at 5%w/v and is mixed gently for 1-2min to ensure the complete mixing of the cryoprotectant BQCA-SA-P80-NPs dispersion. These vials were placed in the pre-freezer shelf, where the temperature was reduced at a rate of 1°C/min, to -40°C at atmospheric pressure for 145 min. Following pre-freezing, the pressure was slowly reduced to 150 µbar, and the temperature was increased to -30°C very gradually, for 23 h. The residual moisture content was removed by slowly increasing the shelf temperature to 20°C and at a rate of 1°C/min, and 130 µbar pressure for 21h. Finally, nitrogen gas was purged over the samples, and the vials were closed with rubber stoppers and were stored at 4°C, until further analysis or usage.

S 1.2.1 SEM and TEM analysis

SEM analysis was performed at 20kV as an accelerating voltage. BQCA-SA-P80-NPs suspension (5-7 mg) was spread uniformly on stubs made of aluminium and was allowed to settle; after this, the excess liquid was removed by paper bolting. A thin layer (150 A°) of gold was coated on the particles using a sputter coater, making the sample conductive. The samples were then analyzed with SEM instrument (27, 28). TEM analysis was performed at 200 kV and employing a negative staining

method. After diluting the sample with double distilled water in the ratio of 1:100., the sample was placed onto 200-mess copper grids coated with carbon. The samples were negatively stained by addition of a drop of phosphotungstic acid (2% w/v) and allowed to stain for 0.5 min, the excess stain was cleared off by paper bolting. The gird was air-dried to form a thin film of the sample, at room temperature. The grids were analyzed under TEM instrument.

S1.3 Stability Studies

Stability study of the BQCA-SA-P80-NPs suspension and lyophilized BQCA-SA-P80-NPs, as per the ICH Guidelines, ICH Q1 A (R2), at varying temperatures and relative humidity 5±3°C; 25±2°C/65±5% RH and 40±2°C/75±5% RH for a period of 6 months. At time intervals of 0, 1, 3 and 6 months, the BQCA-SA-P80-NPs were analyzed for changes in PS, ZP, PDI. Drug content was analyzed only at the end of 6months period (36, 37)

S1.4 Composition of aCSF

Composition of aCSF- Solution A consisted of sodium chloride (8.66g),potassium chloride (0.224g), calcium chloride (0.206g) and magnesium chloride (0.163g), in 500 ml distilled water. Solution B consisted of disodium hydrogen phosphate (0.214g) and disodium dihydrogen phosphate (0.027g) in 500 ml distilled water. These two solutions were mixed in 1:1 ratio (35).

S1.5 *In vitro* drug release studies for an optimized batch of BQCA-SA-P80-NPs

The study was performed on the suspension of nanoparticles within 24 h of preparation using a dialysis membrane (Molecular weight cut off 12000 -14000 Daltons). BQCA-SA-P80-NPs dispersion or naïve BQCA solution (equivalent to 5 mg of BQCA) was dialyzed against 500 ml of dissolution medium (aCSF added with 10 µM of amidase solution) which was stirred at a speed of 100 rpm and was maintained at 37 ±0.5°C. Evaporative losses during the experiment were prevented by covering the beaker with aluminum foil. Samples (0.5 ml) were withdrawn at predetermined time intervals of 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and 48 h and were analyzed for drug content as per the previously developed LC-MS method. Sink conditions were maintained throughout the study, by replacing the sample withdrawn with fresh dissolution media, at every time point. All measurements were made three times, and the values were cumulative drug release.

S 1.6 Hemolysis assay

Blood was freshly collected into heparinized tubes, from rats by retro-orbital puncture and was centrifuges at an rpm of 1500 for 10min to collect red blood cells (RBC) pellet. The RBC pellet was washed with ice-cold phosphate buffer saline (PBS), thrice, and centrifuged. The formed RBC pellet was re-dispersed in PBS. Cell suspensions of 5% v/v with PBS are prepared from the stock. Erythrocyte suspensions were incubated with BQCA-SA-P80-NPs at concentrations of 5-500 µg/ml at 37°C for one hour. After one hour, the tubes are centrifuged as 1500 rpm for 10 minutes to separate the supernatant. 100 µL of the supernatant was added with 2 ml of 99% ethanol/hydrochloric acid (HCl) (39:1 v/v) mixture to dissolve all components other than hemoglobin. At the end of the study,

the supernatant was removed, and the absorbance was measured at 398 nm**.** The percentage of hemolysis was determined using the following formula

$$\% \, Hemolysis = \frac{A_s - A_1}{A_2 - A_1} \, X \, 100$$

Cells incubated with 0.1% SDS serves as positive control and cells incubated with PBS as negative control Where, A_s is the sample absorbance, A_1 and A2 are the absorbances of the negative control and positive control respectively

S 1.7 SRB Assay

The SH-SY5Y cells were grown as a monolayer in Dulbecco's Modified Eagle's medium (DMEM) in a 60 mm cell culture dish; cells were passaged when 75% confluent by trypsinization (300 µL of 0.05% trypsin-0.02% EDTA solution) and seeded at approximately 10,000 cells per well in sterile, polystyrene 96-well plates (Costar®, USA). After 24h, the cells were treated with 5-500 µg/ ml at of BQCA-SA-P80-NPs. After 24 and 48h time intervals, cell viability was determined using the sulforhodamine-B (SRB) assay. Briefly, the cells were treated with 100 µl of cold 10% trichloroacetic acid (TCA) and were incubated at 4°C for 1 h. The TCA solution was then discarded, and the cells were washed three with milli-Q water followed by drying under nitrogen. 50 µL of 0.2% SRB dye was added to each well and incubated for 30 min. The SRB dye was then discarded, and the cells were washed with 1% acetic acid and dried. After complete drying, 200 µL of cold 10 mM Tris buffer (pH 10.5), was added to each well and the plate is shaken over a gyratory shaker for 10 min to dissolve the protein-bound dye and absorbance was measured at 510 nm (Perkin Elmer EnSpire™ Multimode Plate Reader)

Percentage cell viability was calculated using formula

$$\% \text{ Cell viability} = \frac{\text{absorbance of sample}}{\text{absorbance of control}} \text{X100}$$

S 1.8 Surgical procedure

The surgical area was sterilized with 70% ethanol and shaved. A precise incision of 2-3 mm was made along the midline of the scalp. The incision was further extended to 1.0 to 1.5 cm using fine sharp scissors to expose sagittal suture. Points of bregma and lambda were located and using stereotaxic apparatus; points were marked at -1.0 ± 0.06 mm posterior to bregma (towards lambda), 1.8 ± 0.1 mm lateral to the sagittal suture, each side. Holes were made on the skull, the located points. STZ (3mg/kg) was injected with Hamilton syringe at a flow rate of 0.5 ml/min using a stereotaxic apparatus. aCSF, instead of STZ was injected for the sham group using the same procedure. Postoperative monitoring was performed to prevent infections and to ensure a complete recovery

S1.9 Western Blotting

Lysis buffer comprising 20 mM NaH2PO4, 50mMNaF, 2mM EDTA, 150mMNaCl, 1% deoxycholic acid, 0.1% SDS, pH 7.2 was used to prepare whole cell lysates for western blot analysis (Lin et al., 2005). Protease inhibitor cocktail (Sigma Aldrich, Mumbai) was used for western blot analysis. The

protein (40 mg) was separated using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The membrane was incubated with antibodies against anti-APP, anti-tau, anti-NF-kB, anti-BACE, anti-tubulin) (Cell Signalling, Danvers, MA, USA) and horseradish peroxidase-conjugated goat anti-rabbit IgG was used as the secondary antibody. This was later detected using chemiluminescence reagents.

S2. RESULTS

S2.1 Lyophilization of BQCA-SA-P80-NPs

The results were given in **Table S9**. Lyophilization of optimized BQCA-SA-P80-NPs, using mannitol, as a cryoprotectant, slightly increased the PS and ZP of the formulation. However, a slight decrease in PDI was observed.

S2.2 Stability studies

The results were given in **Table S10.** The effects of temperature and humidity on the stability of the formulation were assessed based on ICH guidelines. It was observed that the freeze-dried BQCA-SA-P80-NPs showed better stability with respect PS, ZP and PDI up to 6 months when compared to BQCA-SA-P80-NP suspension. When stored at 25±2°C/65±5% RH, PS of BQCA-SA-P80-NP suspension was found to increase form 166.62±1.24 nm to 186.64±1.98 nm, by the end of 6 months, whereas, the freeze-dried formulation showed only a minimal increase from 171.98±2.01 nm to 173.57±1.87 nm. In case of ZP, BQCA-SA-P80-NP suspension showed an increase of ZP for 23.59±0.37 mV to 25.97±0.70 mV, whereas the freeze-dried formulation showed increase of ZP for 24.27±0.12 mV to 25.27±1.54 mV. The increase in PS and ZP was found to more prominent at 40±2°C/75±5% RH for BQCA-SA-P80-NP suspension. The changes in drug content were found to be minimal at all temperature and humidity conditions. However, both BQCA-SA-P80-NPs and lyophilized BQCA-SA-P80-NPs stored at refrigerated conditions (5±3°C) showed minimal changes in particle size and zeta potential as compared to the formulation stored at room temperature. Based on the results obtained, it was observed that the freeze-dried formulation was stable for more than six months at refrigerated conditions.

S3. The optimized formulation was selected using the desirability criterion (near to 1).

S 3.1 Effect of independent variables on PS

The model for PS generated by the software was found to be significant with F-value of 214.19 and R^2 value of 99.74%. The effect of each linear, quadratic and interactive terms can be established from ANOVA and pareto charts, where the significance of the terms is represented by P-value ($p<0.05$). The linear terms of surfactant concentration (A), sonication amplitude (B) and sonication time (C), interactive terms of AC and square terms of A, B have significant effects on the particle size ($p<0.05$) were included in the final polynomial equation. The polynomial equation obtained for this model for PS is

PS (nm)= 568.4 - 41.78 A - 7.476 B- 5.49 C+ 4.553 A^2+ 0.04813 B^2+ 0.751 A*C

In the above regression equation, where the positive sign represents synergistic effects and the negative sign denotes antagonistic effects. From the main effects plots, we can observe that all the three independent variables have a significant effect on PS. However, this effect is more significant with surfactant concentration and sonication amplitude. The effect of the independent variable on PS can be further observed from 3D surface plots

S3.2 effect of independent variables on ZP

The ANOVA results for PS of BQCA-SA-P80-NPs were given in The model for PS generated by the software was found to be significant with F-value of 303.98 and R^2 value of 99.82%. The effect of each linear, quadratic and interactive terms can be established from ANOVA and pareto charts where the significance of the terms is represented by P-value ($p<0.05$). The linear terms of surfactant concentration (A), sonication amplitude (B), and sonication time (C),, interactive terms of AB, BC and square terms of B,C have significant effects on the ZP ($p<0.05$) and were included in the polynomial equation. The polynomial equation obtained for this model for ZP is

ZP (mV) = -12.752 + 0.5071 A 0.2481 B+ 1.1722 C + 0.001890 B*B- 0.07546 C*C - 0.005125 A*B- 0.002667 B*C

From the main effects plots, we can observe that all the three independent variables have a significant effect on ZP. However, this effect is more significant with sonication amplitude and sonication time. The effect of the independent variable on ZP can be further observed from 3D surface plots

S4. LC-MS Method Development for BQCA

S4.1 Chromatographic condition

A triple quadrupole mass spectrometry (waters TOF) with electrospray ionization (ESI) interface, LC20AD pump, CTO-20AC column oven, CMB-2 site controller, and SIL 20 AC autosampler and a lab solution data were used for data acquisition. The separation was attained using a Zorbax C_{18} column (10mm x 4.6 mm, 3µ particle size) using the mobile phase of ammonium formate (10 mM, pH 6.0 adjusted with 0.1 % formic acid) and methanol (80:20, v/v) at the flow rate of 0.8 ml/min as mobile phase. The detection of both BQCA and internal standard (IS), 1-[[2-Fluoro-4-(1-methylpyrazol-4-yl) phenyl] methyl] indole-2,3-dione (VU0366369), was achieved using positive electrospray ionization. The following are the set mass working parameters: heat block temperature (400°C), capillary voltage (1.4 kV), desolvation line temperature (300°C), Ultra-pure nitrogen (15 L/min) and argon (250 kPa) were used as the carrier gas and for collision-induced dissociation.

S4.2 Preparation of Quality control samples and Calibration standards

Working solutions used as calibration and controls were prepared by adequately diluting the stock solution (1 mg/ml) with methanol. Calibration standards of BQCA (10-1000 ng/ml) along with IS (500 ng/ml). The quality control samples were prepared in bulk at a concentration of 10, 500 and 1000 ng/ml representing low, medium, and high-quality control samples, respectively.

S4.2.1 Chromatographic Conditions

The detection of both BQCA and IS was done at positive electrospray ionization mode monitored at m/z of 309.90 > 121.15 (BQCA) with collision energy (CE) -18 and 381.00>46.10 (IS) with collision energy (CE) -12, respectively. **Figure S1** shows that the loss of sodium molecule in case of BQCA (m/z 310.0) and the adduct formation of solvent methanol in IS (m/z 381.10). Further, the separation of BQCA and IS was achieved on a Zorbax C18 column (10mm x 4.6 mm, 3µ particle size). Initially the chromatographic separation was performed using different mobile phases [formic acid (0.1%), ammonium acetate (5–10 mM) and ammonium formate (5–10 mM, pH 5.0–8.0) with water] and organic phases (methanol and acetonitrile) in different ratios. A good mass detection was achieved using ammonium acetate (10 mM, pH 5.5) and methanol (30: 70 v/v), however, the analyte peaks were not symmetric. Despite the change in the mobile phase ratio, we were unable to achieve peak symmetry. Hence, further trials were carried out with ammonium formate buffer as it provided symmetric peaks while adjusting pH (5.0-8.0) and concentration (5.0-10 mM) to achieve mass resolution. After repeated trials, use of ammonium formate (10 mM, pH 6.0) and methanol (80:20, v/v) at a flow rate of 0.8 ml/min, which produced a highly sensitive method with a run time of 3 min. The retention time of BQCA and IS were 1.35 and 1.34 min, respectively. The standard chromatograms of BQCA and IS were shown in **Figure S2.**

S4.2.2 Method validation

The developed method for the estimation of BQCA in BQCA-SA-P80-NPs was validated as per the ICH guidelines (216). The method was validated for specificity, accuracy, precision, linearity, the limit of detection, and quantification. The accuracy of the method was determined intra-day and inter-day accuracy studies at three quality control samples (n=6) and the results obtained were found to be within limits, which was set at 15% of the nominal concentration (**Table S1**). The precision of the method was determined by recovery studies in which the mean peak area obtained from extracting the analytes from BQCA-SA-P80-NPs with the peak obtained from the standard solution of analytes (**Table S1).** The linearity of the method was plotted by response versus concentration of the standard solution. The correlation coefficient of BQCA were found to be > 0.999 with a regression equation of $y = 0.0028x + 0.0016$, **Figure S3.** Further, the limit of detection (LOD) and the quantification (LOQ) were determined at the signal to noise ratio of 3:1 and 10:1, respectively. The limit of detection and limit of quantification for BQCA were found to be 5 ng/ml and 10 ng/ml, respectively.

Table S1. Accuracy and precision results of BQCA

Analyte	QC samples (ng/ml)	Mean conc. found (ng/ml) ± SD	Intra-day		Inter-day	
			Accuracy	% RSD	Accuracy	% RSD
BQCA	10	8.7 ± 0.26	88.00	4.30	86.33	6.37
	500	488.2 ± 7.63	97.66	1.56	95.80	3.51
	900	878.0 ± 10.01	99.03	1.23	97.18	2.80

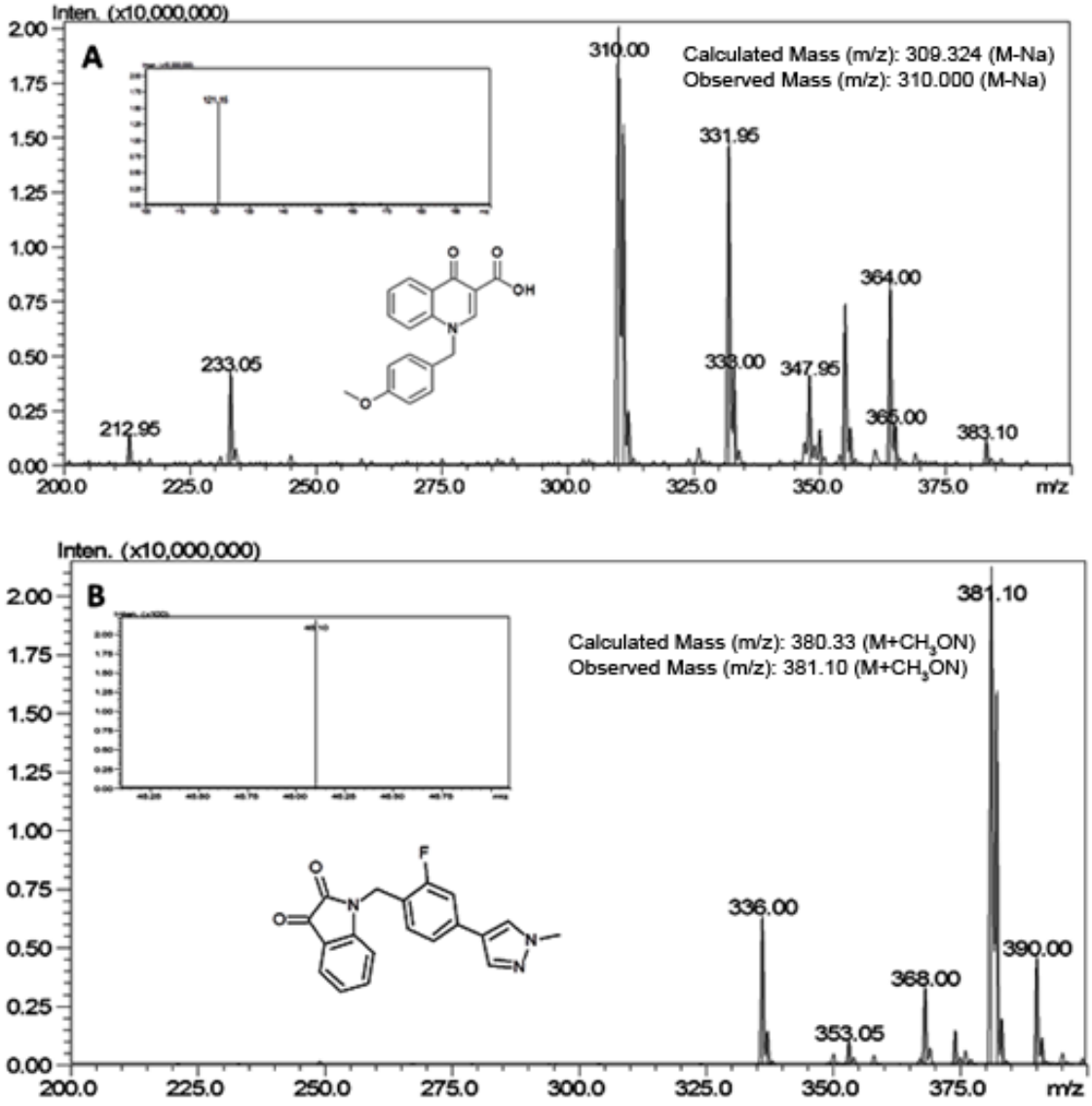

Figure S1. Mass scan spectra and product ion spectra (image showed inside the box) of (A) BQCA (B) Internal standard (IS)

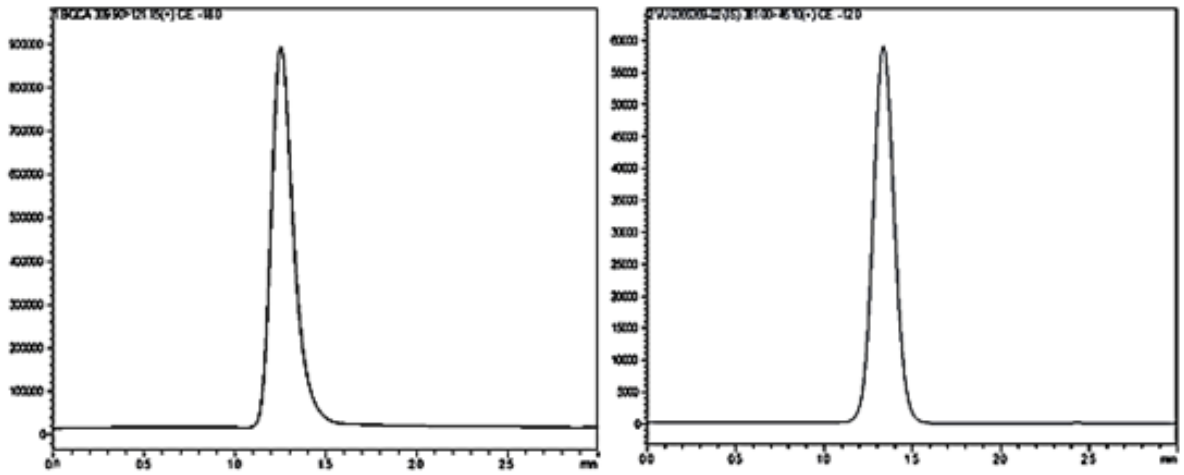

Figure S2. LC-MS/MS chromatograms of Standard (BQCA) and IS (VU0366369)

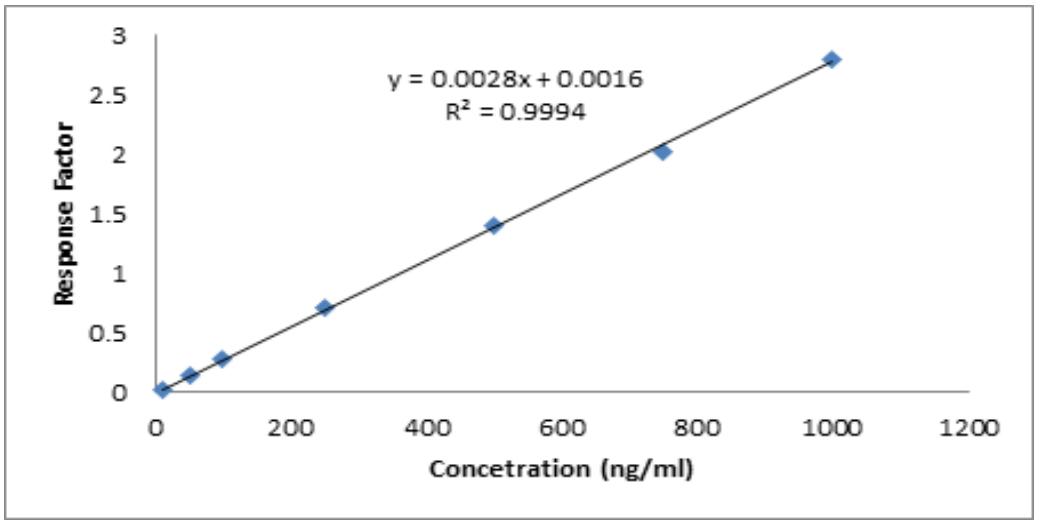

Figure S3. Linearity plot for BQCA

Analytical method developed for BQCA using LC-MS was found to be accurate, precise and rapid for the quantification of BQCA in the formulation **(Figure S1,S2).** The developed method was validated as per ICH guidelines for linearity, accuracy (recovery), precision (inter-day and intraday) studies, and were found to be with in the acceptable limits (**Table S1),** with a correlation coefficient, R^2 of 0.999 for linearity ranging between10-1000 ng/ml **(Figure S3)**

Table S2. Responses for the dependent variables for 15 Experimental batches

Std Order	Run Order	Surfactant Concentration (%w/v)	Sonication Amplitude (%)	Sonication Time (min)	PS (nm)	ZP (mV)
12	1	4	100	9	176.58±1.34	21.79±0.35
5	2	2	80	3	199.85±2.07	23.13±0.26
15	3	4	80	6	165.26±1.58	22.22±0.84
11	4	4	60	9	167.59±2.83	22.17±0.53
14	5	4	80	6	165.33±2.29	22.24±0.62
7	6	2	80	9	166.07±1.53	22.92±0.48
9	7	4	60	3	189.65±1.08	22.77±0.55
4	8	6	100	6	204.35±3.22	21.18±0.59
10	9	4	100	3	198.64±1.05	21.75±0.34
1	10	2	60	6	200.42±1.46	22.12±0.42
8	11	6	80	9	173.31±1.57	22.68±0.87
3	12	2	100	6	209.41±2.54	20.99±1.04
13	13	4	80	6	164.18±3.21	22.21±0.27
2	14	6	60	6	195.36±2.54	21.49±0.53
6	15	6	80	3	189.07±2.07	22.79±0.45

The values are mean ± S.D., (n=3)

Table S3. Analysis of Variance data of response surface quadratic model for Particle Size of BQCA-SA-P80-NPs

Source	Adj MS	F-Value	P-Value	
Model	424.74	214.19	< 0.05	Significant
Linear	616.55	310.91	< 0.05	
A- Surfactant Concentration	1227.43	618.95	< 0.05	
B-Sonication Amplitude	39.19	19.76	< 0.05	
C-Sonication time	583.04	294.01	< 0.05	
Square	820.01	413.51	< 0.05	
A^2	1224.50	617.47	< 0.05	
B^2	1368.35	690.01	< 0.05	
C^2	4.14	2.09	0.208	
2-Way Interaction	27.06	13.65	< 0.05	
AB	0.00	0.00	1.000	
AC	81.18	40.94	< 0.05	
CB	0.00	0.00	1.000	
Error	1.98			
Lack-of-Fit	3.03	7.29	0.123	Non-Significant
Pure Error	0.42			
Regression Analysis				
R^2	99.74 %			
Adjusted R^2	99.28 %			
Predicted R^2	96.16 %			

Table S4. Analysis of Variance data of response surface quadratic model for Zeta Potential of BQCA-SA-P80-NPs

Source	Adj MS	F-Value	P-Value	
Model	0.62720	303.98	< 0.05	Significant
Linear	0.25644	124.28	< 0.05	
A- Surfactant Concentration	0.00602	2.92	< 0.05	
B-Sonication Amplitude	0.72461	351.18	< 0.05	
C-Sonication time	0.03869	18.75	< 0.05	
Square	1.37892	668.30	< 0.05	
A^2	0.00031	0.15	0.871	
B^2	2.18443	1058.69	< 0.05	
C^2	1.63693	793.34	< 0.05	
2-Way Interaction	0.09100	44.10	< 0.05	
AB	0.16810	81.47	< 0.05	
AC	0.00250	1.21	0.334	
CB	0.10240	49.63	< 0.05	
Error	0.00206			
Lack-of-Fit	0.00328	14.07	0.143	Non-Significant
Pure Error	0.00023			
Regression analysis				
R^2	99.82%			
Adjusted R^2	99.49%			
Predicted R^2	97.19%			

Table S5. Stability data for BQCA-SA-P80-NP suspension and lyophilized formulation

Sampling time	BQCA-SA-P80-NPs Suspension			Freeze dried BQCA-SA-P80-NPs		
	5±3°C	25±2°C/65±5% RH	40±2°C/75±5%RH	5±3°C	25±2°C/65±5% RH	40±2°C/75±5%RH
			Particle Size (nm)			
Initial	166.62±1.24	166.62±1.24	166.62±1.24	171.98±2.01	171.98±2.01	171.98±2.01
1 month	169.48±3.36	171.45±2.24	178.47±3.14	172.12±1.98	172.98±1.48	172.48±2.78
3 months	172.48±2.37	177.54±2.87	194.58±2.43	172.86±3.14	173.24±2.54	173.64±1.64
6 months	175.89±3.64	186.64±1.98	211.56±2.25	173.01±2.42	173.57±1.87	174.22±3.27
			Zeta Potential (mV)			
Initial	23.59±0.37	23.59±0.37	23.59±0.37	24.27±0.12	24.27±0.12	24.27±0.12
1 month	24.06±0.49	24.48±0.84	24.44±0.12	24.78±0.42	24.95±0.97	24.66±0.74
3 months	24.98±0.64	25.04±0.53	25.57±0.62	24.91±0.37	25.12±0.84	25.22±0.59
6 months	25.12±0.53	25.97±0.70	26.32±0.44	25.19±0.29	25.27±1.54	25.54±0.86
1			Polydispersity Index			
Initial	0.397±0.021	0.397±0.023	0.397±0.020	0.382±0.014	0.382±0.014	0.382±0.014
1 month	0.404±0.015	0.411±0.010	0.434±0.027	0.382±0. 011	0.384±0.017	0.385±0.009
3 months	0.410±0.018	0.418±0.015	0.474±0.022	0.385±0.008	0.389±0.023	0.389±0.015
6 months	0.413±0.013	0.422±0.017	0.505±0.014	0.386±0.010	0.390±0.019	0.392±0.021
			Drug Content (%)			
6 months	97.20±1.57	95.52±2.47	95.14.20±2.53	97.24±1.48	96.97±1.92	96.52±2.75

Table S6. Results of Predicted and Experimental batches of Optimized BQCA-SA-P80-NPs

	Predicted Value	Experimental Value	Prediction Error
PS (nm)	163.85	166.62 ± 1.24	1.69±0.75
ZP (mV)	22.90	23.59± 0.37	3.03±1.63

The values are mean ± S.D., (n=3)

Table S7. *In vitro* release data for optimized BQCA-SA-P80-NPs

Time (h)	Percentage Drug Release (%)	
	naïve BQCA solution	BQCA-SA-P80-NPs suspension
0.5	10.57±1.98	6.60±0.75
1	27.29±2.86	8.66±1.72
2	40.07±3.07	16.91±2.54
4	65.76±1.34	26.67±1.87
6	80.82±2.54	33.82±1.52
8	98.79±1.55	39.01±1.19
12		45.35±2.03
16		57.48±2.68
20		66.15±1.60
24		72.19±2.57
48		86.31±2.27

The values are mean ± S.D., (n=3)

Table S8. *In vitro* release kinetic data for optimized BQCA-SA-P80-NPs

Release Kinetics	R^2
Zero-Order	0.843
First -order	0.977
Higuchi	0.976
Korsmeyer-Peppas	0.984
	n = 0.601

Table S9. PS, ZP and PDI of optimized batch of BQCA-SA-P80-NPs before and after lyophilization

	Before Lyophilization	After lyophilization
PS (nm)	166.62 ± 1.24	171.98±2.01
ZP (mV)	23.59 ± 0.37	24.27±0.12
PDI	0.397 ± 0.21	0.382±0.014

The values are mean ± S.D., (n=3)

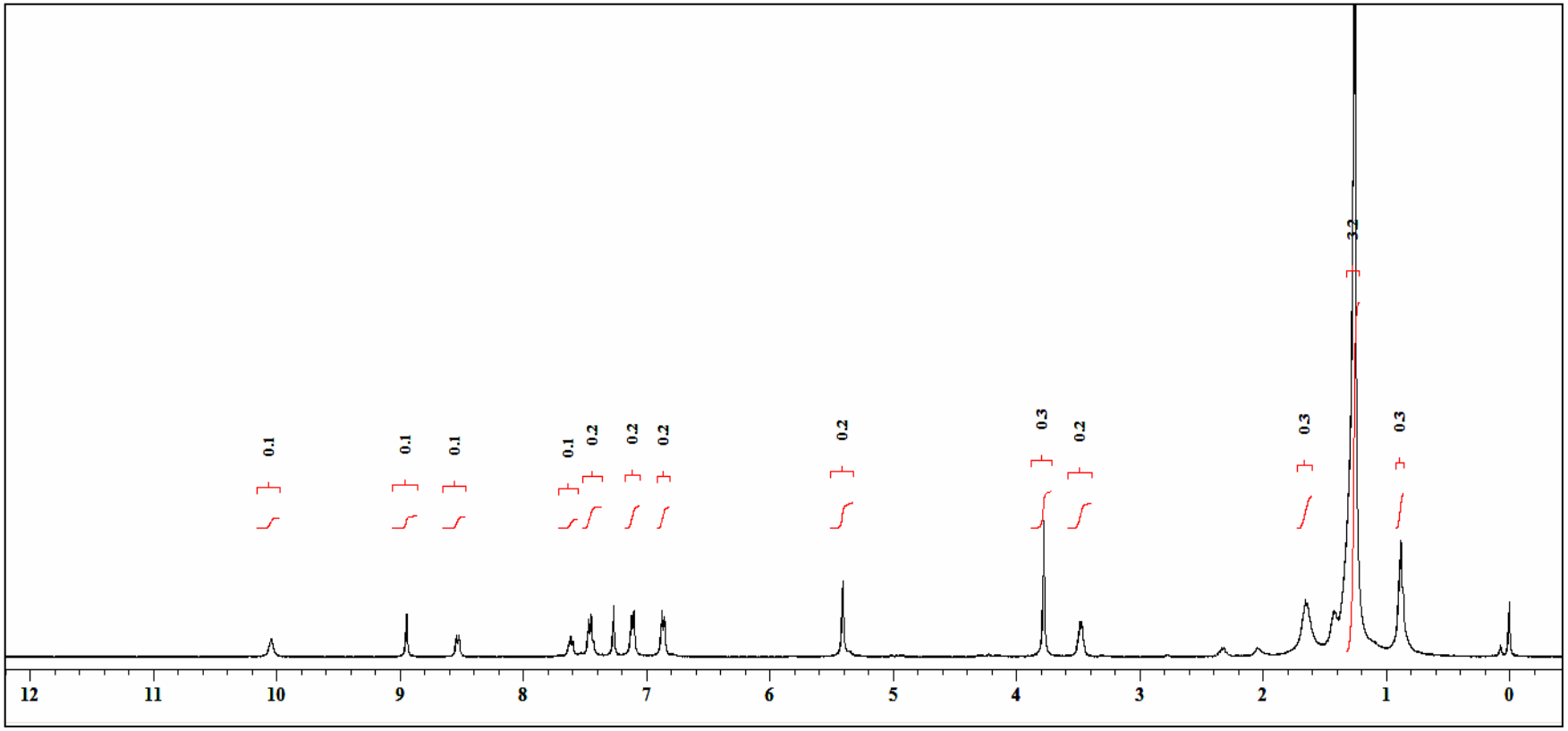

Figure S4. H[1]NMR of BQCA-SA LDC

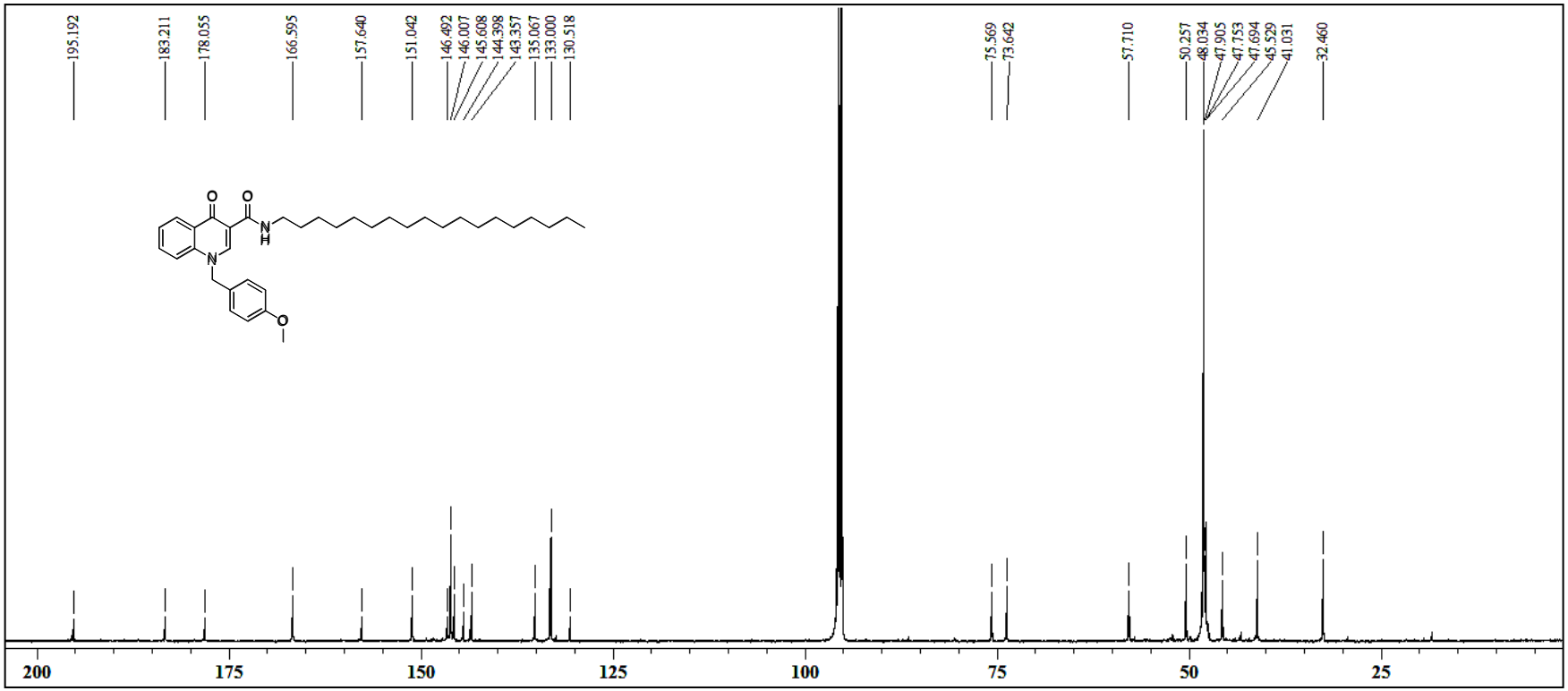

Figure S5. ^{13}C NMR of BQCA-SA LDC

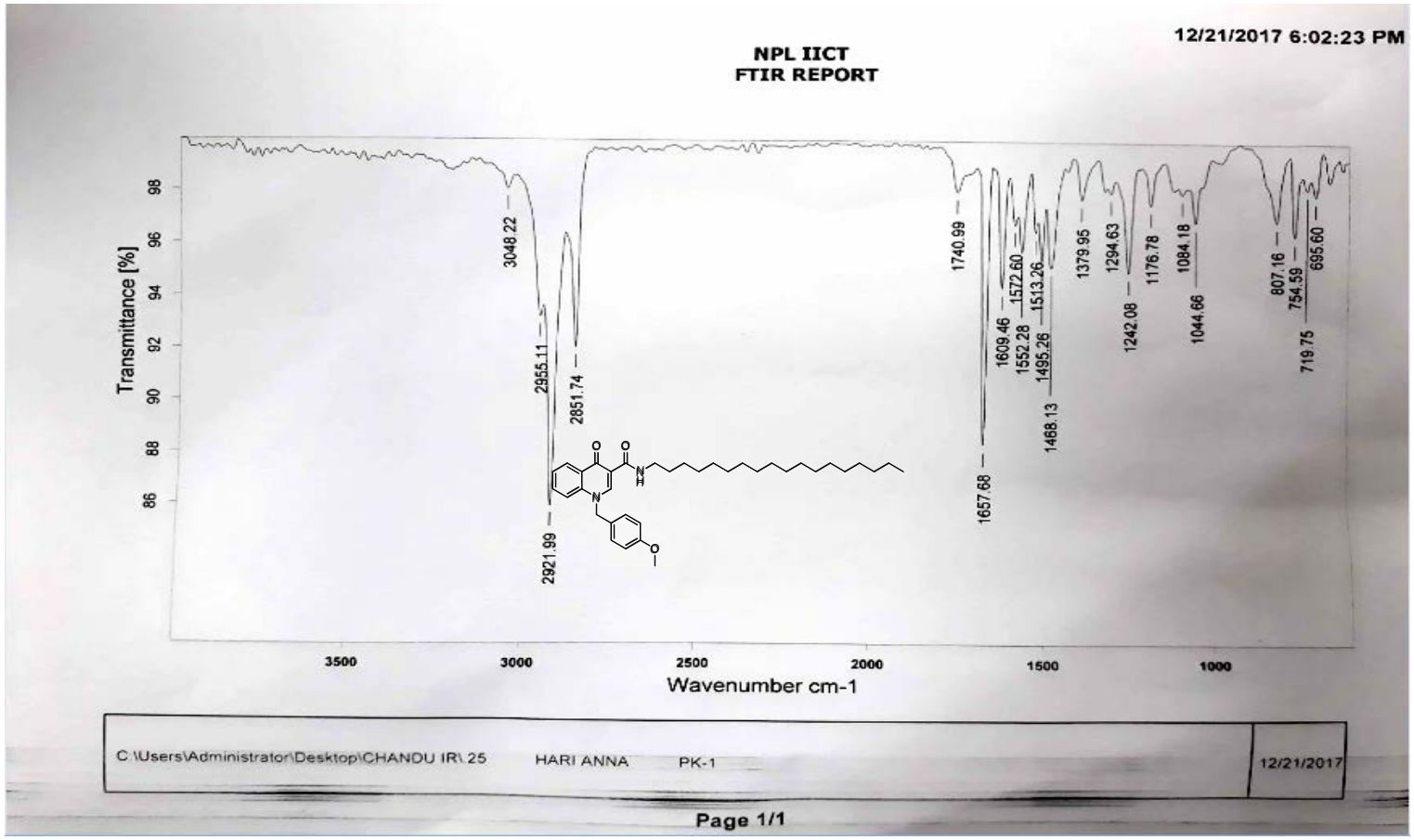

Figure S6. FT-IR Spectrum of BQCA-SA LDC

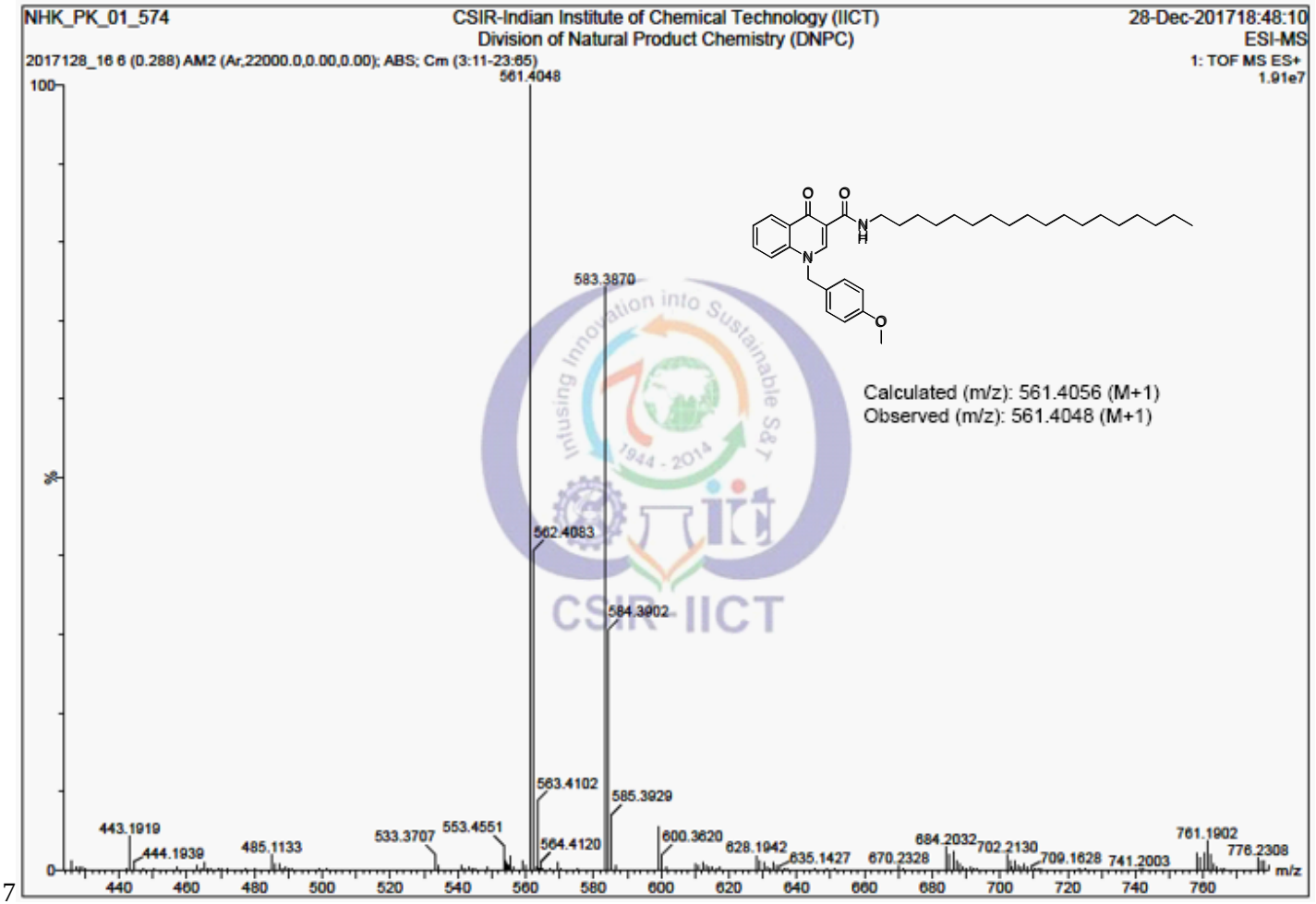

Figure S7. HRMS Spectra for BQCA-SA LDC

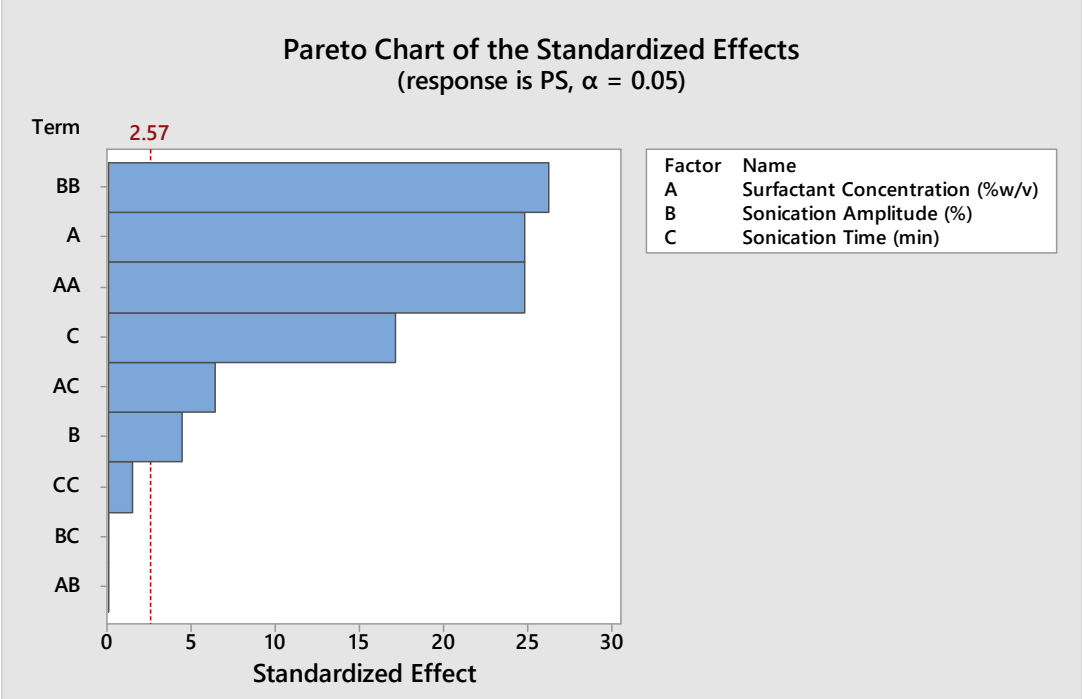

Figure S8. Pareto Charts of the Standard effects on PS of BQCA-SA-P80-NPs

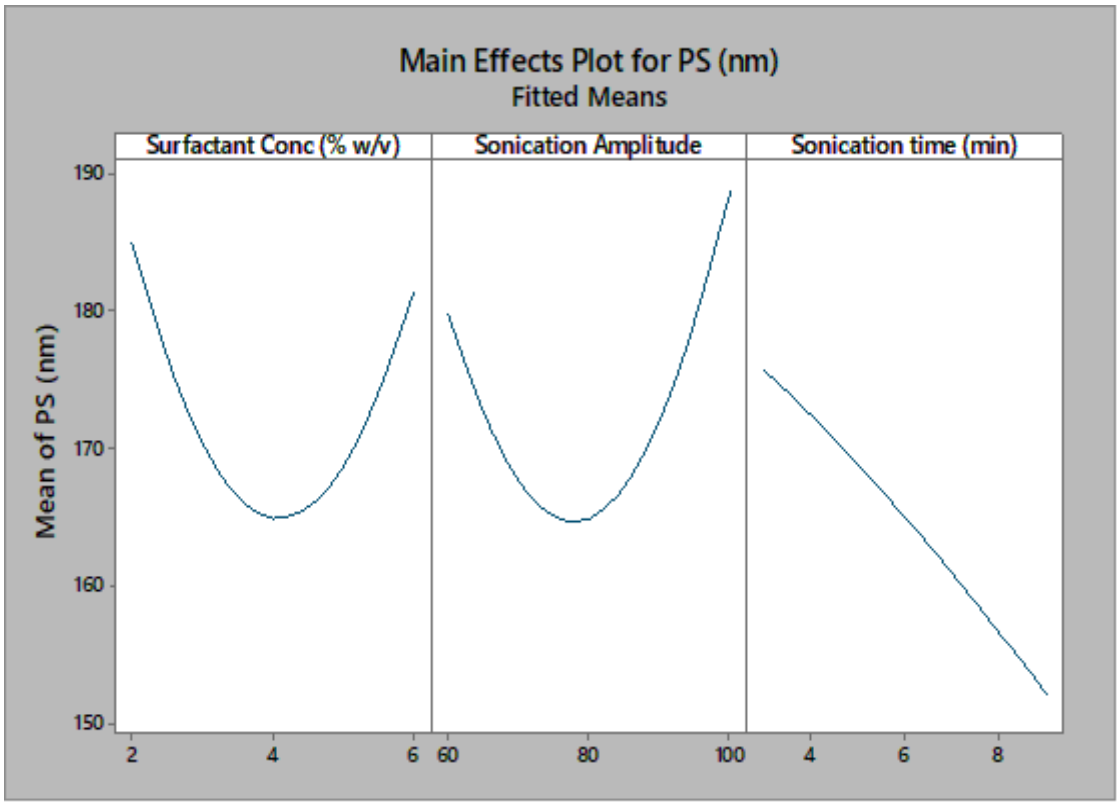

Figure S9. Main effect Plots of surfactant concentration, sonication amplitude and sonication time on PS of BQCA-SA-P80-NPs

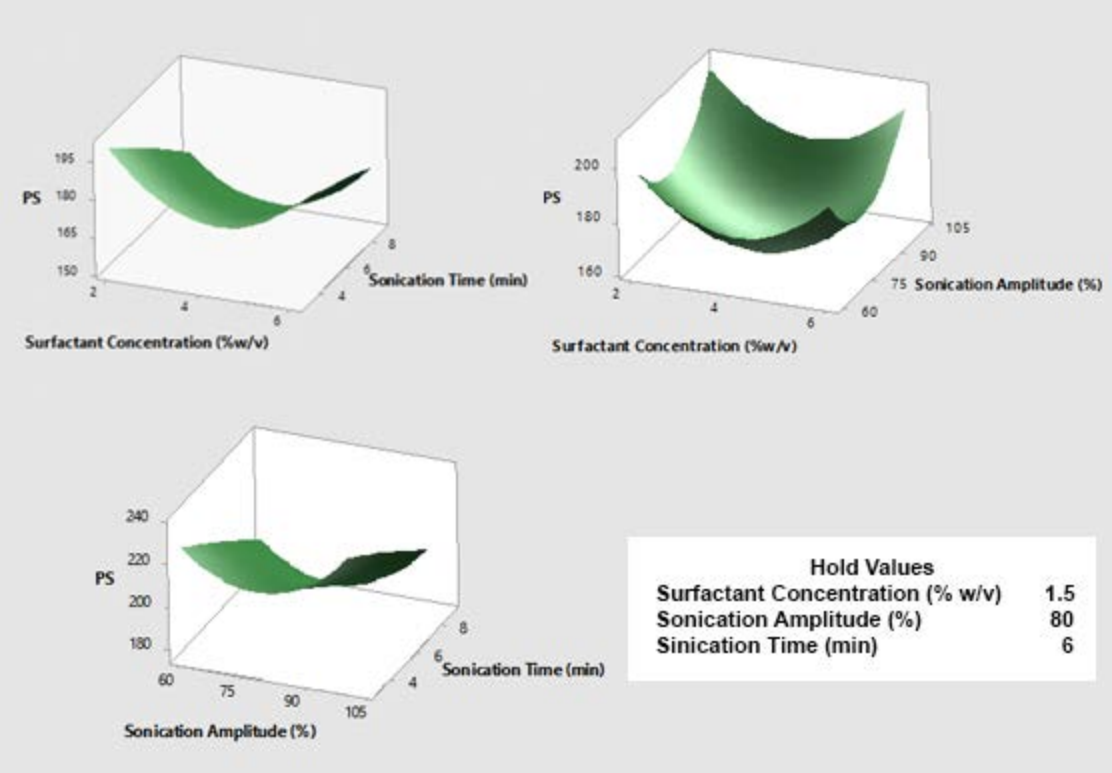

Figure S10. Response surface plots showing the effects of surfactant concentration, sonication amplitude and sonication time on PS of BQCA-SA-P80-NPs

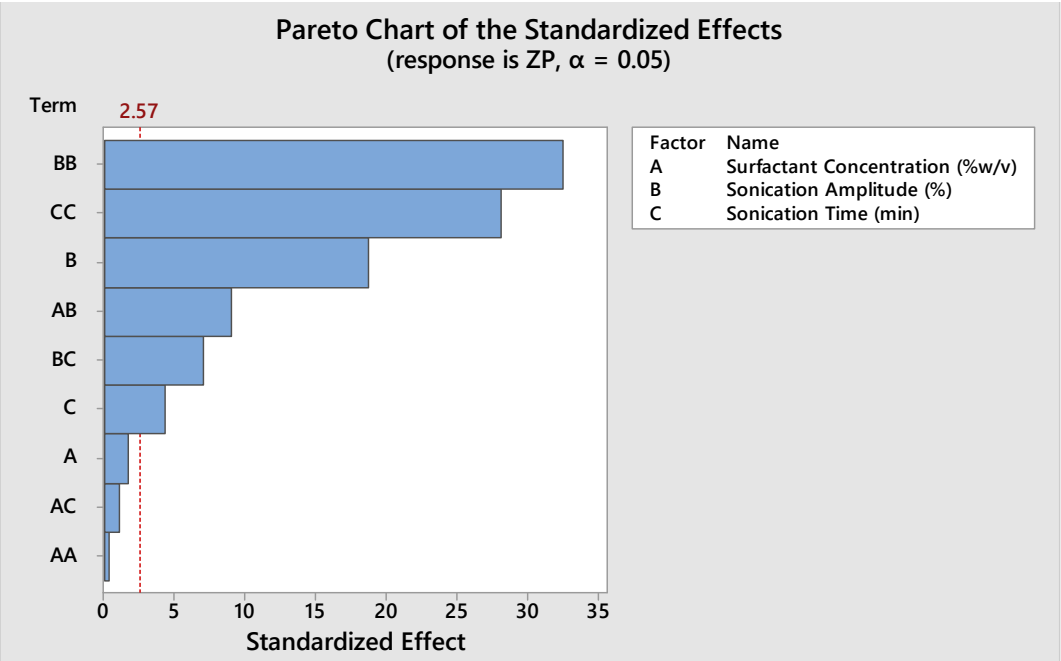

Figure S11. Pareto Charts of the Standard effects on ZP of BQCA-SA-P80-NPs

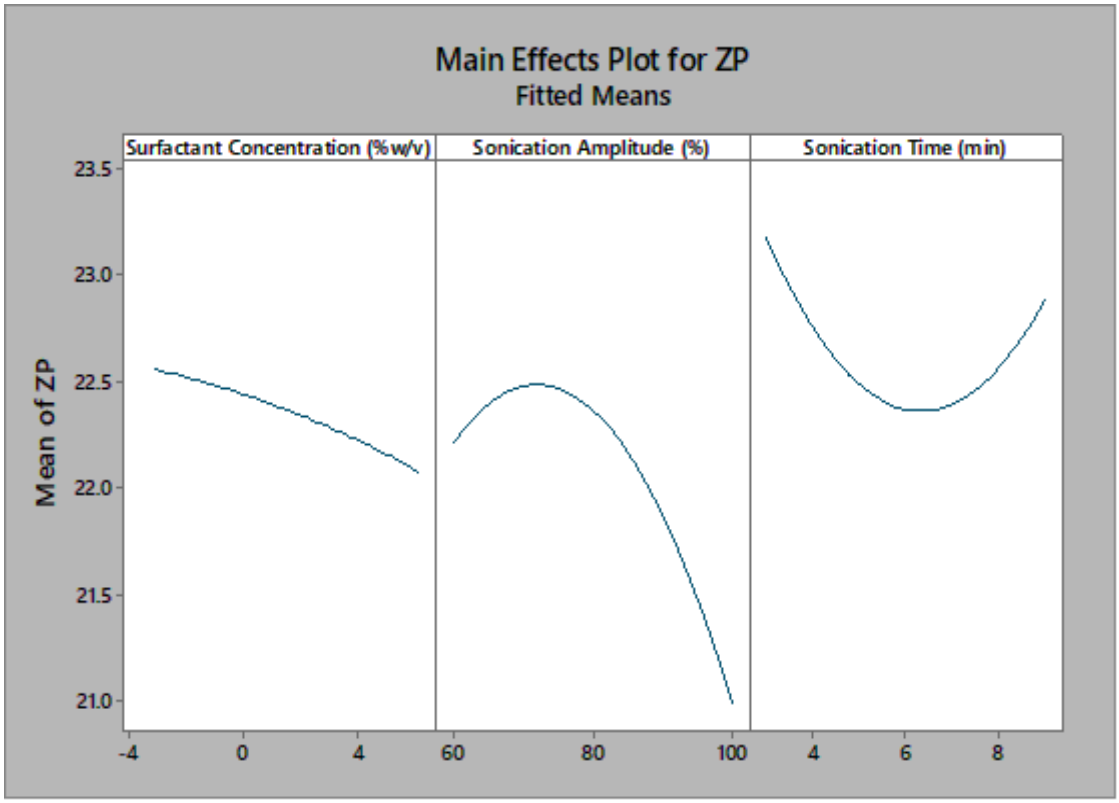

Figure S12. Main effect Plots of surfactant concentration, sonication amplitude and sonication time on ZP of BQCA-SA-P80-NPs

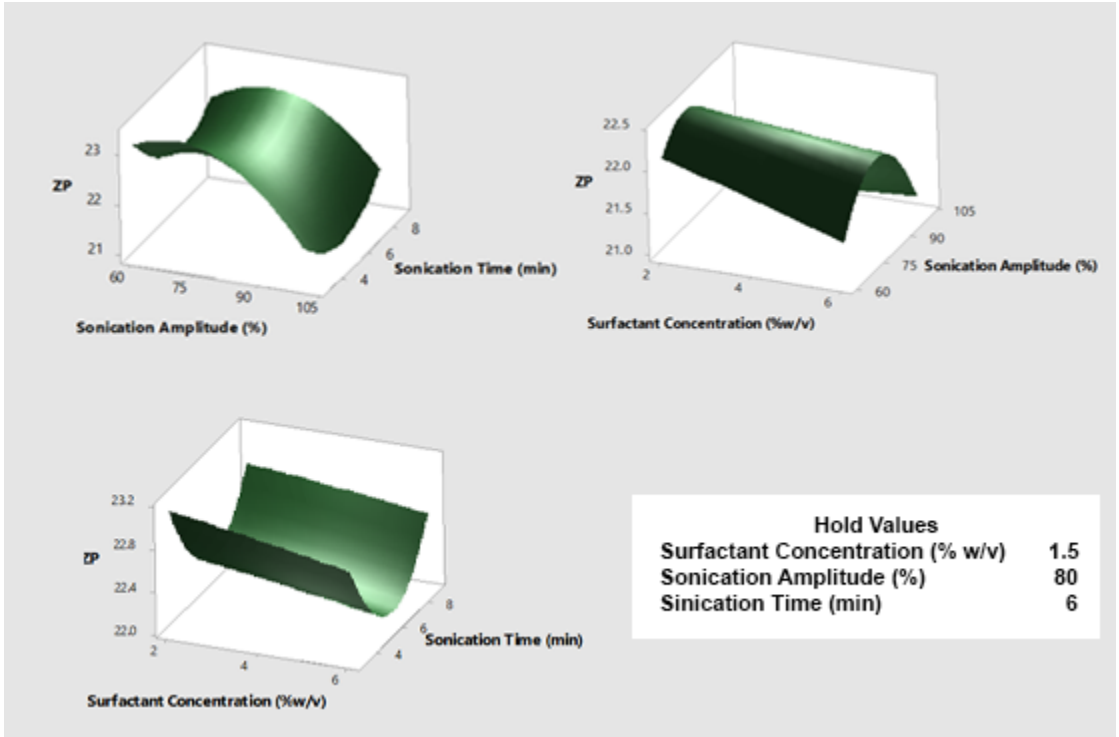

Figure S13 . Response surface plots showing the effects of surfactant concentration, sonication amplitude and sonication time on ZP of BQCA-SA-P80-NPs

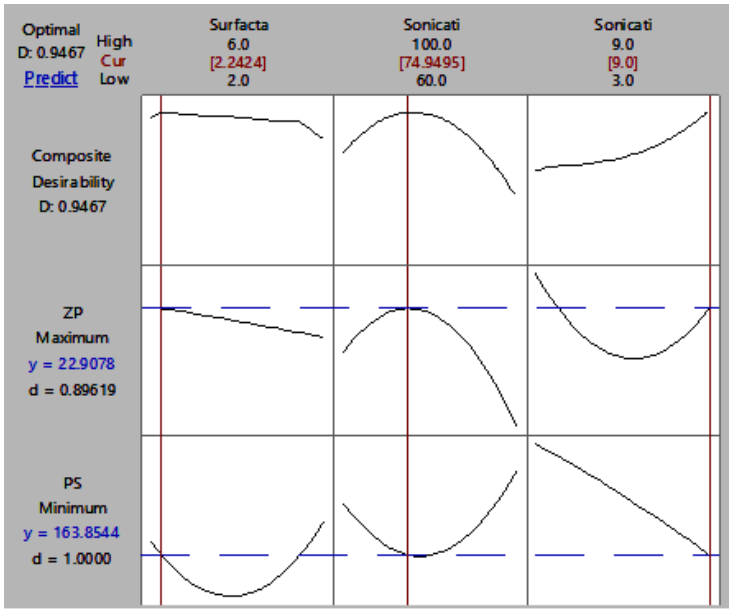

Figure S14 Response Optimization: PDI, Zeta Potential (mV), Particle Size (nm) Parameters

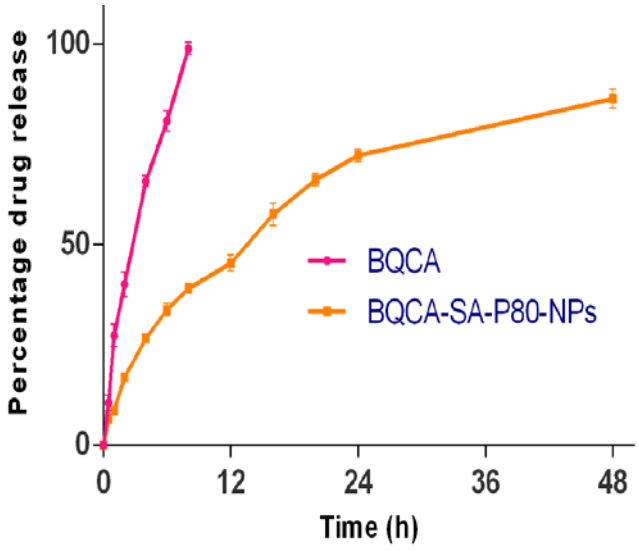

Figure S15. *In vitro* drug release plot for BQCA and BQCA-SA-P80-NPs

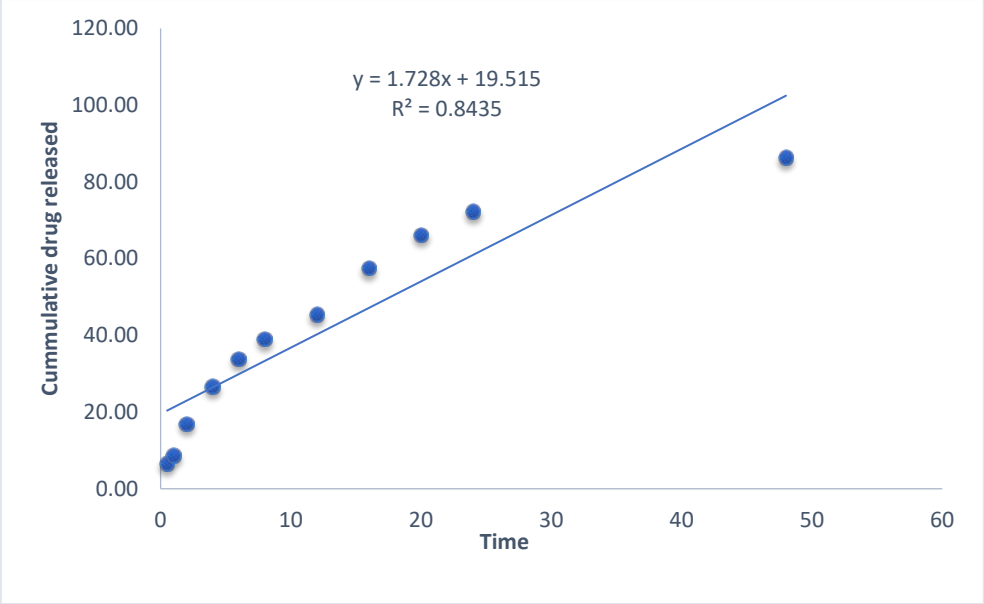

Figure S16. Zero-order Plot for Optimized BQCA-SA-P80-NPs

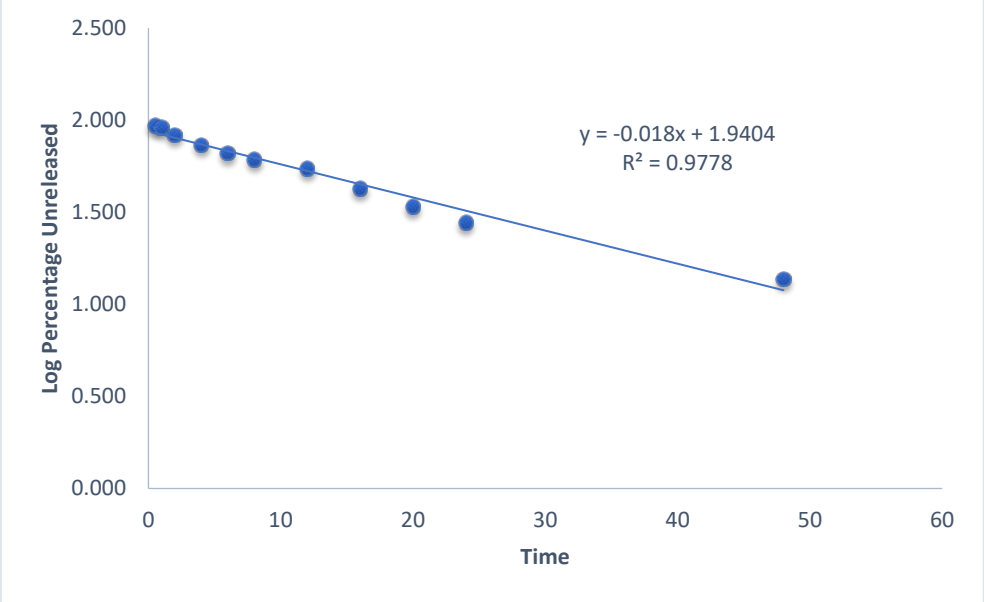

Figure S17. First-order Plot for Optimized BQCA-SA-P80-NPs

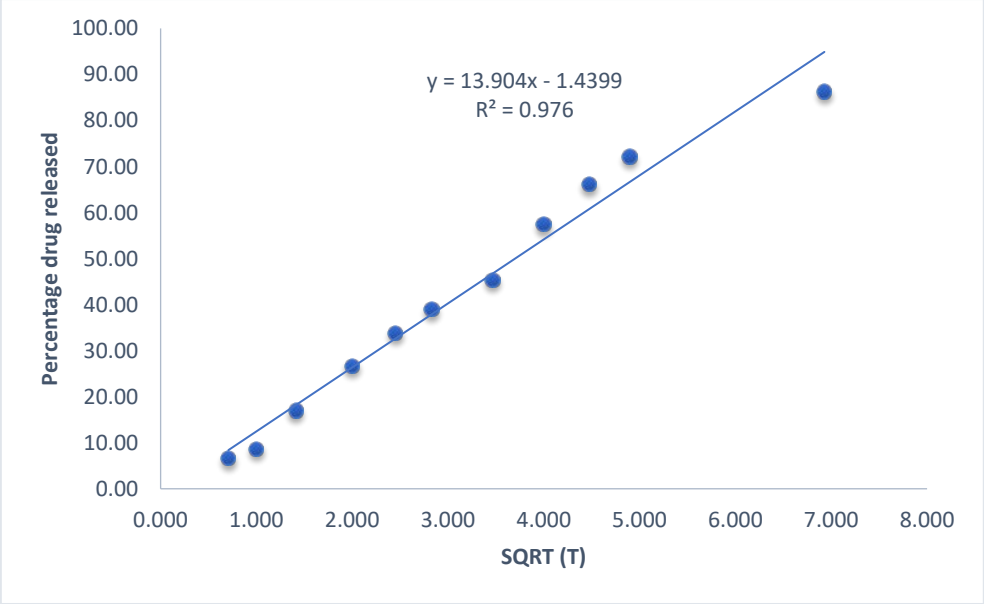

Figure S18. Higuchi Plot for Optimized BQCA-SA-P80-NPs

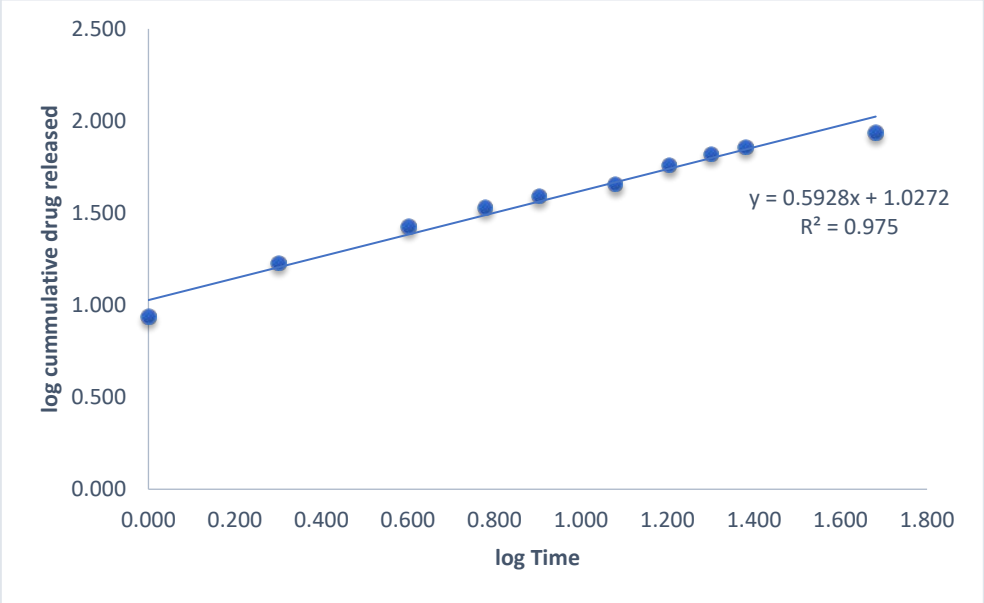

Figure S19. Korsmeyer-Peppas Plot for Optimized BQCA-SA-P80-NPs