**Synthesis and characterization of poly(propylene imine)-dendrimer-grafted gold
nanoparticles as nanocarriers of doxorubicin**

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Abstract

The aim of current work is synthesis 4th-generation-poly(propylene imine) (PPI)-dendrimer modified gold nanoparticles (Au-G4A) as nanocarriers for doxorubicin (DOX) and studying in vitro drug release kinetics from nanocarriers into different media. Accordingly, AuNPs were synthesized by reduction of chloroauric acid (HAuCl₄) aqueous solution with trisodium citrate and modified with cysteamine to obtain amine-functionalized (Au-NH₂) nanoparticles. Au-NH₂ nanoparticles were used as multifunctional cores and participated in Michael addition of acrylonitrile and reduction process by lithium aluminum hydride (LAH) to synthesize Au-G4A nanoparticles. Also, peripheral primary amine groups of Au-G4A were conjugated with folic acid (FA) (Au-G4F) to study the bioconjugation effect on drug release behavior of nanostructures. Ultraviolet spectroscopy (UV-visible), atomic force microscopy (AFM), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FT-IR), and thermal gravimetric analysis (TGA) were used to approve the synthesis of different nanostructures. Finally, Au-G4A and Au-G4F samples were loaded with DOX and exposed to environments with different pH values to examine the release properties of nanostructures. Also, drug release kinetics was investigated by fitting of experimental data with different release models. As a result, synthesized dendritic structures showed Higuchi and Korsmeyer-Peppas models release behavior due to better solubility of drug in release media with respect to dendrimer cavities and drug release through polymeric matrix respectively.

Keywords: Gold nanoparticles; Poly(propylene imine) dendrimer; Doxorubicin; Drug release kinetics

1. Introduction

Gold nanoparticles (AuNPs) as non-toxic and biologically compatible nanoparticles have gotten increasing attention in different fields such as biomedical [1], hybrid nanomaterials [2], etc. Also, Surface Plasmon resonance (SPR) as a unique optical property is conferred by the interaction of light with electrons on the surface of gold nanoparticles [3]. These have resulted in application of AuNPs in different drug delivery systems [4-5]. Beside this, dendrimers as three-dimensional, highly-branched and monodispersed polymeric nanostructures have been used in drug delivery systems [6-7]. They are synthesized via an iterative sequence of reactions such as Michael addition, alkylation and reduction [8-9]. Poly(propylene imine) (PPI) dendrimer as an amine-terminated dendrimer is synthesized via Michael addition of acrylonitrile to an amine-capped core and subsequent reduction of nitrile groups to primary amines by reduction catalysts [10]. However, due to cytotoxicity of dendrimers originated from peripheral amine groups, surface primary amine groups have been conjugated with biocompatible compounds such as folic acid (FA) [11] and polymeric chains [12]. In this field, FA is one of the most promising candidates with the potential for cancer-cell specific targeting due to its high affinity for folate receptors (FRs) [13]. However, conjugation of FA with PPI dendrimers may affect the drug release behavior of dendrimers.

Nowadays, different works have been reported about PPI dendrimer/gold hybrid nanoparticles [14-16]. In some cases, they have been utilized as catalyst for reduction of phenol derivatives [14] whereas in other cases they have been used in cancer therapy [15-16]. However, no work has reported the generation growth from the surface of AuNPs as well as drug release kinetics from these hybrid nanoparticles even in FA-conjugated or -nonconjugated forms. On the other hand, PPI dendrimers can also be used to modify AuNPs to enhance their therapeutic properties via

improvement of the cytocompatibility and cellular uptake [16]. Furthermore, attaching dendrimer onto the surface of nanoparticles results in easy purification process [17].

In this work, AuNPs have been prepared by reduction of HAuCl_4 with trisodium citrate and subsequent reaction with cysteamine. Then, amine-functionalized AuNPs have been used as multifunctional cores and acrylonitrile has been added to amines via Michael addition reaction to prepare half-generation-PPI-modified AuNPs. To reduce nitrile groups to primary amines, a hydrogenation process by lithium aluminum hydride (LAH) has been utilized until 4th-generation PPI dendrimer has been grafted onto surface of nanoparticles. Also, effect of FA conjugation with peripheral amine groups on drug release behavior of hybrid nanoparticles has been investigated. Finally, doxorubicin (DOX) as an anti-cancer drug was loaded onto different synthesized hybrid nanoparticles and its release behavior has been studied in different conditions. Also, release kinetics has been studied by fitting of release data with different drug release models.

2. Experimental Section

2.1. Synthesis of Au nanoparticles

Gold powder (0.860 g) was dissolved in 800 mL of 3:1 (v/v) mixture of concentrated HCl and HNO_3 at 300 °C to obtain HAuCl_4 . After evaporation of solvent, HAuCl_4 was diluted to 20 L with distilled water to achieve 0.2 mM aqueous solution of HAuCl_4 .

Turkevich method was used to synthesize the colloidal AuNPs via reduction of HAuCl_4 by trisodium citrate [18]. Accordingly, an aqueous solution of HAuCl_4 (150 mL, 0.2 mM) was heated to the boiling temperature and aqueous solution of trisodium citrate (50 mL, 1.8 mM) was added

to reaction media. In a few seconds, bluish color appeared due to formation of gold nuclei. Then, in a few minutes, the solution turned red-wine color because of the formation of nanoparticles.

2.2. Synthesis of cysteamine-functionalized gold nanoparticles (Au-NH₂)

AuNPs were functionalized with cysteamine by adding 0.2 M aqueous solution of cysteamine hydrochloride to colloidal AuNPs. Accordingly, 1 mL aqueous solution of cysteamine was added to 150 mL colloidal AuNPs and reaction was continued for 20 min at room temperature and darkness. Au-NH₂ nanoparticles were separated and purified by several centrifugations at 10000 rpm for 30 min and drying in vacuum at 40 °C overnight.

2.3. Synthesis of PPI-dendrimer-grafted AuNPs

To graft nitrile-terminated first generation of PPI dendrimer (G1N) onto surface of AuNPs, a previously described divergent method was used with some modifications [19]. To this end, Au-NH₂ (1.0 g, containing 2.4 mmol amine moieties per 1.0 g of Au-NH₂) was used as an initial core and dispersed in deionized water (10 mL) via ultrasonication (30 min). ACN (0.8 mL, 12.0 mmol) was added dropwise at room temperature and dark room condition during 1 h to participate in Michael addition reaction. Reaction was continued for 1 h and then, media was heated to 80 °C and reaction was continued for more 1 h to complete the addition reaction. The obtained suspension was centrifuged (10000 rpm) and washed with water three times. Finally, the remaining ACN and solvent was removed under vacuum at 50 °C for 48 h to obtain Au-G1N nanoparticles.

To obtain amine-terminated first generation of PPI-dendrimer-grafted AuNPs (Au-G1A), nitrile groups were reduced to primary amines via a homogeneous reduction method by LAH.

Accordingly, Au-G1N (1.0 g, containing 2.4 mmol nitrile moieties per 1.0 g of Au-G1N) was dispersed in diethyl ether (20 mL) via ultrasonication (30 min) and a mixture of LAH (0.19 g, 5 mmol) in diethyl ether (60 mL) was added dropwise and reaction was continued for 4 h at 34 °C. Then, reaction mixture was placed in ice-water bath and deionized water (10 mL) was added dropwise and stirring was continued for 1 h. After separating diethyl ether, an aqueous solution of HCl (pH = 3) was added to aqueous media to dissolve salts produced during reaction. The reaction mixture was then filtered via 0.22 µm PTFE membrane filter and dried under vacuum at 50 °C for 48 h to obtain Au-G1A. Scheme 1 shows the reaction route to achieve Au-G1A nanoparticles. PPI-dendrimer-grafted AuNPs up to fourth generation were prepared by repetition of all the above steps consecutively, with increasing quantity of ACN and subsequently LAH. Also, reaction time of Michael addition was increased 1 h per each generation increase.

Scheme 1: The reaction route to achieve Au-G1A nanoparticles

2.4. Conjugation of FA with surface of Au-G4A nanoparticles

Firstly, Au-G4A was reacted with glycidol to achieve Au-G4OH via previously described method [20-21]. Au-G4A (0.2 g) was dispersed in methanol (10 mL) via ultrasonication (30 min). A solution of glycidol (0.14 mL) in methanol (10 mL) was added dropwise to reaction media and the mixture was stirred at 60 °C under nitrogen for 24 h. The mixture was centrifuged and obtained powder was washed with methanol and centrifuged three more times. Finally, product was dried under vacuum at 50 °C for 48 h.

To synthesize FA-conjugated nanoparticles (Au-G4F), a previously described method with some changes was utilized [22]. FA (0.28 g), DCC (0.133 g) and DMAP (0.026 g) were dissolved in

DMSO (10 mL) and Au-G4OH (0.2 g) was dispersed in media via ultrasonication (30 min). Then, the mixture was stirred for 72 h at 50 °C and centrifuged to obtain Au-G4F. To further purification, product was washed with water and centrifuged three more times and dried under vacuum at 50 °C for 48 h. Scheme 2 shows the route that we used to achieve Au-G4F nanoparticles.

Scheme 2: The route to achieve Au-G4F nanoparticles

2.5. Encapsulation of DOX in Au-G4A and Au-G4F dendrimers

Aqueous solution of DOX (1 mg/mL, 6 mL) was mixed with Au-G4A or Au-G4F dendrimer (24 mg), and the solution was tuned to the desired pH with subsequent shaking for 48 h in dark conditions. The DOX-loaded nanoparticles were separated by centrifugation and the loaded drug content was obtained from the drug concentrations before and after loading by means of UV-visible absorption at 480 nm.

2.6. *In vitro* drug release studies

The DOX-loaded Au-G4A or Au-G4F aqueous solutions (4 mg/mL, 5 mL) in cellulose dialysis bag (MWCO = 12000) were submerged in phosphate-buffered saline (PBS, 100 mL) stirring at 200 rpm (37 ± 2 °C) for 48 h at two pH values (5.3 and 7.4). At predetermined intervals of time, 1-mL aliquots were withdrawn and replaced with an equal volume of fresh medium. The DOX concentrations were determined by UV-visible absorption at 480 nm according to a pure DOX calibration curve.

2.7. Instrumentation

Ultraviolet visible (UV-vis.) absorptions from liquid samples were recorded on a Perkin-Elmer Lambda 9 instrument. Samples were analyzed immediately after completion of reactions. Atomic force microscopy (AFM) images were recorded using a AFM apparatus from Ara Pajouhesh Co., Iran. The scanning probe microscope (SPM) was equipped with a silicon cantilever, which was operated in the tapping mode. A droplet of colloidal Au nanoparticles (modified or unmodified) was deposited on freshly cleaved mica slide. The droplet was then carefully washed after allowing the sample to sit for about 10 minutes. To dry the sample before scanning, it was left 2 h in a dust protected heater. To calculate particle size and particle size distribution, BELView 6.2 was used as free image processing software considering about 50 individual nanoparticles. A transmission electron microscope (TEM), Tescan Mira, with an accelerating voltage of 120 kV was used to study the morphology of hybrid nanoparticles. All the samples were prepared by a drop-dry method on carbon-coated copper grids. Fourier transform infrared (FT-IR) spectroscopy was performed by means of a Bruker Tensor 27 FT-IR spectrophotometer, in the range between 500 and 4000 cm^{-1} with a resolution of 4 cm^{-1} . An average of 24 scans has been carried out for each sample. The samples were prepared on a KBr pellet in vacuum desiccators. Thermal gravimetric analyses (TGA) were carried out by means of a PL thermo-gravimetric analyzer (Polymer Laboratories, TGA 1000, UK). All samples (about 10 mg) were heated from ambient temperature to 700 $^{\circ}\text{C}$ at a heating rate of 10 $^{\circ}\text{C}/\text{min}$ and nitrogen as the purging gas was used at a flow rate of 50 mL/min .

3. Results and discussion

3.1. Preparation and surface modification of AuNPs

The addition of cysteamine to colloidal AuNPs gives cysteamine-stabilized AuNPs (Au-NH₂) due to formation of Au-S covalent bond [23]. Figure 1 shows the UV-vis. spectra of AuNPs and Au-NH₂ nanoparticles. The characteristic peak of AuNPs appears at 520 nm and indicates the formation of stable gold nanoparticles with diameter of 15.8 nm according to the equation 1 [24]:

$$d(nm) = 2.99\lambda_{max} - 1539 \quad (1)$$

where, d and λ_{max} are diameter of nanoparticles and wavelength of the peak respectively. After treatment with cysteamine, characteristic peak of UV-vis. shifts to 522 nm and broadens due to coupled Plasmon resonance and indicates attachment of the cysteamine onto AuNPs surface [25].

Figure 1: UV-vis. spectra of AuNPs and Au-NH₂ nanoparticles

Particles size and particle size distribution of AuNPs and Au-NH₂ nanoparticles are calculated using AFM images as shown in Figure 2. The number average particle size (D_n), weight average particle size (D_w), and polydispersity (PDI) are calculated according to the equations (2)-(4) [26].

$$D_n = \frac{\sum_{i=1}^n n_i D_i}{\sum_{i=1}^n n_i} \quad (2)$$

$$D_w = \frac{\sum_{i=1}^n n_i D_i^4}{\sum_{i=1}^n n_i D_i^3} \quad (3)$$

$$PDI = \frac{D_w}{D_n} \quad (4)$$

where, n_i and D_i are the number of nanoparticles and diameter respectively. According to the results of AuNPs, D_n , D_w , and PDI are 14.4 nm, 15.8 nm and 1.097 respectively. This shows that nanoparticles have narrow size distribution and results agree UV-vis. data. Also, D_n , D_w , and PDI of Au-NH₂ nanoparticles are calculated 14.8 nm, 16.1 nm and 1.088 respectively. This shows that treatment of AuNPs with cysteamine does not affect the particle size and particle size distribution as proved by UV-vis. results.

Figure 2: AFM images and particle size distributions of AuNPs and Au-NH₂ nanoparticles

The morphological study of Au-NH₂ nanoparticles and PPI-dendrimer-grafted AuNPs (Au-G4A) was performed by TEM images. As shown in Figure 3, AuNPs have spherical shape and individual nanoparticles are observed. Also, Au-G4A results in a spherical-like shape and a core-shell structure originated from a slightly deep contrast of core and a light contrast of shell. This arose from the different mass contrasts between the Au core and dendritic shell.

Figure 3: TEM image of Au-NH₂ and Au-G4A nanoparticles

The FT-IR spectra of different modified AuNPs are depicted in Figure 4. According to the results, Au-NH₂ nanoparticles exhibited a characteristic peak of cysteamine at 1465 cm⁻¹ originating from the N-H vibration of NH₂ groups [27] and a peak at 1315 cm⁻¹ related to C-S bond [28]. Peaks at 1629 and 1040 cm⁻¹ are ascribed to -OH of water molecules [29] and C-N vibration [30]. Also, peaks at 2850, and 2930 cm⁻¹ are related to the methyl-stretching bonds [31] and the peak at 3400 cm⁻¹ is ascribed to the O-H stretching of water molecules absorbed into sample [32]. In Au-G4N, Michael addition reaction of ACN and -NH₂ groups results in disappearance of characteristic peak of amine groups at 1465 cm⁻¹ and appearance of a new peak at 2220 cm⁻¹ related to nitrile groups of half-generation PPI dendrimer [33]. After reduction of nitrile groups to primary amines, peak at 2220 cm⁻¹ disappears and peaks at 3260, 3130 and 1454 cm⁻¹ related to primary amines appears again. Conjugation of FA onto the surface of nanoparticles leads to appearance of peaks at 1690 and 1626 cm⁻¹ related to amide bonding within FA structure [34] and peaks at 3050 and 1576 cm⁻¹ due to aromatic rings of FA structure [35]. Also, peak at 3330 cm⁻¹ is ascribed to the amine groups within the structure of FA [36].

Figure 4: FT-IR spectra of different modified AuNPs

TGA were also performed on the modified Au nanoparticles to prove the success of grafting process as shown in Figure 5-A. Also, TGA results are summarized in Table 1. According to the results, Au-NH₂ nanoparticles showed 18.50 wt. % mass loss (120-700 °C) whereas mass loss of dendrimer-grafted AuNPs increased exponentially with increasing dendrimer generation as depicted in Figure 5-B ($y = 23.1442e^{0.4066x}$, where y is the weight losses (%) and x is the number

of the generation, $R^2 = 0.9118$). This is the best proof of successful grafting of PPI dendrimers onto the surface of AuNPs [37-38]. Moreover, grafting density (GD) of grafted PPI dendrimers was calculated based on Equation (5) in each modification step [39]:

$$GD \left(\frac{\text{mol}}{\text{g of Au}} \right) = \frac{\left(\frac{W_i - W_{i-1}}{100 - W_i} \right)}{M} \quad (5)$$

where, W_i , W_{i-1} and M are mass losses (120-700 °C) and molecular weight of degradable moiety added in each modification step respectively. According to the results, GD of cysteamine groups was calculated 3.0 mmol/g of Au and grafting density increased exponentially to 48.2 mmol/g of Au for Au-G4A nanoparticles (Table 1). When GD is plotting versus generation, an exponential increment of GD versus generation progression is observed ($y = 2.9719e^{0.6949x}$, where y is the GD (mmol/g of Au) and x is the number of the generation, $R^2 = 0.9999$). In this case, exponent of the equation is 0.6949 that is so close to the ideal exponent (0.6931). Conclusively, dendrimer growth from the surface of AuNPs has been occurred ideally and synthesis has been progressed successfully.

Figure 5: A) TGA thermograms of Au-NH₂, Au-G1A, Au-G2A, Au-G3A, and Au-G4A; B)

Weight loss and GD versus generation progression for modified AuNPs

Table 1: Summarized TGA results of modified AuNPs

Sample	W _i (wt. %)	GD (mmol/g of Au)
Au-NH ₂	18.50	3.0
Au-G1A	39.52	5.9
Au-G2A	64.58	12.0
Au-G3A	85.26	23.7
Au-G4A	96.17	48.2

3.2. Drug loading

Drug loading content (DL) of Au-G4A and Au-G4F were calculated by Equations (6) [40]:

$$DL(\text{mg} / \text{mg}) = \frac{\text{Weight of the drug in nanoparticles}}{\text{Weight of the nanoparticles}} \quad (6)$$

DL was calculated 0.033 ± 0.03 and 0.045 ± 0.02 for Au-G4A and Au-G4F respectively. The amount of drug loading was significantly higher (36.4%) for Au-G4F compared with Au-G4A. This is originated from better interaction of drug with surface terminal groups [6] due to folate conjugation onto the dendrimer surface. Also, noncovalent interactions such as hydrogen bonding and hydrophobic interaction between DOX and PPI dendrimers lead to physical binding of drug molecules inside the core and surface-engineered groups of dendrimer. Moreover, folate conjugation on the dendrimer surface prevents leaving the DOX molecules from system due to steric hindrance [19].

3.3. *In vitro* drug-release studies

To study the feasibility of synthesized hybrid nanoparticles as anti-cancer drug carriers, the *in vitro* release behavior under a simulated physiological condition ($\text{pH} = 7.4$) and an acidic environment ($\text{pH} = 5.3$) was investigated at $37\text{ }^{\circ}\text{C}$ (Figure 6). The results showed no significant burst release for Au-G4A and Au-G4F in each condition. This can be ascribed to the loading of the DOX in the cavities of the dendrimers which act as sink to retain the drug molecules for a long duration. However, free drug showed monophasic rapid release (97.2% in 4 h at $\text{pH} = 5.3$ and 83.1% in 7 h at $\text{pH} = 7.4$). As a result, synthesized hybrid nanoparticles act as drug-retentive nanocarriers for DOX. Also, Au-G4A showed higher drug release percentage compared to FA-conjugated nanocarriers (Au-G4F) at different pH values. This is because of steric hindrance on the dendrimer surface originated from FA conjugation that acts as a barrier to prevent leaving the DOX molecules from system. However, the DOX release was more rapid for both conjugated and nonconjugated nanostructures at lower pH value. The possible reason of this phenomenon is dissolution of DOX water at low pH [41] whereas DOX becomes positively charged and more soluble in and diffuses more easily from the dendrimer structure to aqueous media. Also, at low pH values, dendrimer cavities become positively charged due to existence of tertiary amines.

Figure 6: The DOX release behavior of synthesized hybrid nanoparticles

3.4. Drug release kinetics

Mathematical models are effective tools to investigate the release kinetics of drugs from nanocarriers. Among different models, zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell models are the most well-known models used in variety of systems [42-44]. In

this work, the release kinetics has been investigated using these models. The release kinetics and parameters of each model have been obtained by linear regression analysis and the coefficients of correlation (R^2) have been used to verify the accuracy of the fittings, as shown in Table 2 and Figures S1-S5. According to the regression results, the zero-order, first-order and Hixson-Crowell models are not appropriate models to fit release data through hybrid gold/dendrimer nanostructures due to the source of these models. The zero-order model is useful in slow release kinetics. However, gold/dendrimer hybrid nanoparticles show rapid drug release due to a rapid change in solubility in aqueous media especially at low pH values. Also, the first-order model is applied in porous matrices which are not soluble in release media. Additionally, Hixson-Crowell model can be applied when the surface area and diameter of the drug matrix change with time. None of these three models are the case of study in our work and also, our data show no proper fitting via these systems. However, free drug release systems and drug release from dendritic structures can be fitted by Higuchi and Korsmeyer-Peppas models at both pH values. Korsmeyer-Peppas model is applicable for drug release from a polymeric matrix. Although no polymeric matrix presents in free drug release system, dialysis bag may behave as polymeric matrix in these systems. Also, Higuchi model describes drug dissolution from matrix into release media. Herein, the most important reason for DOX release from the cavities of dendrimers is the better solubility of DOX in release media than main structure of dendrimers. Conclusively, Korsmeyer-Peppas and Higuchi models describes the DOX release behavior from conjugated and nonconjugated samples at different pH values.

Table 2: Mathematical models' correlation coefficients (R^2) and release exponents for Au-G4A and Au-G4F hybrid nanoparticles

Kinetics model	Equation [33-35]	Parameter	Value					
			pH = 5.3			pH = 7.4		
			Free drug	Au-G4A	Au-G4F	Free drug	Au-G4A	Au-G4F
Zero-order	$Q_t = Q_0 + K_0 t^*$	R^2	0.9530	0.901	0.901	0.943	0.912	0.898
		K_0	22.924	1.090	0.944	9.626	0.669	0.500
First-order	$\log C = \log C_0 + \frac{K}{2.203} t$ **	R^2	0.807	0.749	0.758	0.821	0.785	0.748
		K	0.463	0.033	0.037	0.198	0.033	0.033
Higuchi	$f_t = K_H t^{1/2}$ ***	R^2	0.991	0.975	0.973	0.994	0.979	0.973
		K_H	60.960	9.667	8.364	32.069	5.909	4.441
Korsmeyer-Peppas	$\frac{M_t}{M_\infty} = at^n$ †	R^2	0.977	0.970	0.974	0.994	0.983	0.970
		aM_∞	36.224	6.486	4.539	3.334	4.121	3.289
		n	0.805	0.612	0.660	0.523	0.597	0.590
Hixson-Crowell	$Q_t^{1/3} = Q_0^{1/3} + kt^\ddagger$	R^2	0.870	0.812	0.819	0.869	0.837	0.809
		k	0.567	0.036	0.036	0.244	0.030	0.027

* K_0 is the release kinetic constant.

** K is the release kinetic constant.

*** K_H is the Higuchi's release kinetic constant.

† M_t/M_∞ is a fraction of drug released at time t , a is the release rate constant and n is the release exponent.

‡ k is the release kinetic constant.

4. Conclusions

AuNPs with diameter about 15 nm were synthesized and modified with 4th-generation PPI dendrimers. Then, peripheral amine groups were conjugated with folic acid and the effect of bioconjugation on drug release behavior was investigated. UV-vis. spectra, AFM, TEM, FT-IR and TGA results proved the successful synthesis of hybrid nanoparticles. DOX-loaded Au-G4A and Au-G4F samples were exposed to pH variations to investigate the drug release behavior of dendrimer-grafted Au nanoparticles. Drug loading content was found 0.033 and 0.045 (mg of drug/mg of dendrimers) for Au-G4A and Au-G4F nanoparticles respectively. As a result, the amount of drug loading was significantly higher for Au-G4F nanoparticles with respect to Au-G4A nanoparticles due to FA conjugation onto the dendrons' surface. Also, at different pH values, nonconjugated structures show higher cumulative drug release with respect to FA-conjugated systems because of steric hindrance on the dendrimer surface due to FA conjugation that prevents the DOX molecules from leaving the nanoconjugate system. Additionally, by decreasing the pH value of release media, the DOX release was more rapid in conjugated and nonconjugated nanostructures. Also, the release kinetics were studied via different models. As a result, both Higuchi and Korsmeyer-Peppas models were fitted on data to describe the release kinetics of DOX from hybrid gold/dendritic nanostructures.

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