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ORIGINAL CONTRIBUTION

Encapsulation of nanoparticles using linear–dendritic macromolecules

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Abstract Benzyl alcohol and Rose Bengal were loaded and entrapped using linear–dendritic macromolecules by two procedures. In the first procedure, benzyl alcohol was attached to the end functional groups of linear–dendritic macromolecules by ester bonds to afford linear–dendritic–host conjugates. In the second procedure, entrapment was based on physical interactions between Rose Bengal and linear–dendritic macromolecules; this procedure is known as complexation method. Loading and binding capacity of different linear–dendritic macromolecules was investigated using ^{1}H nuclear magnetic resonance (NMR) and UV spectroscopy methods. It was found the loading or binding capacity of linear–dendritic macromolecules depends on their generation, so that higher generations have higher loading or binding capacity. Diameter of nanocarriers was investigated using dynamic light scattering (DLS) experiments, and it was between 16 and 50 nm for different nanocarriers. Release of guest molecules from nanocarriers was evaluated at pH 1, 7.4, and 10.

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Introduction

Dendrimers are a new class of macromolecules which are able to load and transport small molecules such as drugs. They transport drug molecules at least in three ways:

(1) Encapsulation in internal cavity to afford host–guest systems
(2) Attachment to the functional groups to afford dendrimer–guest conjugates
(3) Physical interaction between guest molecule and dendrimer to afford dendrimer–guest complexes

The internal "cavity" of dendritic macromolecules could be used for entrapment of guest molecules to afford host–guest systems [1–12]. There are three strategies for encapsulation of guest molecules by dendritic macromolecules. The first strategy is physical encapsulation which has been reported by Meijer et al. [1, 2]. The second strategy is based on multiple noncovalent chemical interactions, such as hydrogen bonding between guest molecules and the dendritic structure reported by Newkome et al. [3, 4]. The third strategy is interaction between amphiphilic dendritic macromolecules and guest molecules to behave as micelles, which are capable to dissolve various hydrophobic compounds in aqueous solutions [5–12].

The simplest way to prepare dendrimer–drug conjugates is to couple drug molecules directly to the "surface" of the dendrimer. Because of its multiple surface functionalities, one dendrimer molecule is able to transport multiple drug molecules, and the number of drug molecules per conjugate can be varied by using different generations of dendrimers or

by changing the coupling conditions. Poly(amidoamine) (PAMAM) and poly(aryl ether) dendrimers are two types of dendritic macromolecules which are used for preparation the dendrimer–drug conjugates more than other dendritic macromolecules [13, 14]. For example, folic acid and 5-fluorouracil are attached to PAMAM dendrimers to form conjugates [15, 16]. In addition, capability of poly(aryl ether) and peptide dendrimers for delivery of some drugs and model drugs is investigated [17–19]. On the other hand, recently, Gao et al. [20] have reported conjugation of some small guest molecules on the surface functional groups of hyperbranched polymers.

Another way for entrapment and transport of the guest molecules by dendritic macromolecules is complexation. Complexation is different from above-mentioned amphiphilic systems because here, dendrimers are not amphiphilic [21, 22].

However, it is clear that dendrimers are of high interest for application in drug delivery systems. An important factor for all mentioned ways to load and transport drugs by dendrimers is quality of release. An ideal drug-delivery system releases the drug in the desirable time and place. Several independent groups (de Groot et al., Amir et al., and Li et al.) have reported new drug delivery systems based on tailored dendrimers [24–26]. Their goal is to achieve total and simultaneous release of active agents through changing an environmental factor such as pH. In the developed systems by the mentioned groups, effective release of drugs is based on the fact that the dendrimer skeleton can be constructed in such a way that it can be made to disintegrate into known molecular fragments once the disintegration process has been initiated. A brief review about reported works by these groups is published by Meijer and van Genderen [27].

Linear–dendritic macromolecules are hybrid large molecules containing dendrimers and linear polymers. Interesting properties of this type of dendritic macromolecules have stimulated investigation in this area [28–36].

We have reported synthesis of some of linear–dendritic macromolecules and their application for encapsulation and release of some of guest molecules previously [45]. Dendritic citric acid macromolecules are water soluble and biocompatible compounds; hence, they are good candidates for application as drug-delivery systems [46]. In this work, some small guest molecules are delivered using these dendritic macromolecules by two procedures.

Experimental

Materials Poly(ethylene glycol) 600 diacid (acid number 175, 96–98%, from Fluka) was dried over Na_2SO_4. Citric acid and Dicyclohexyl carbodiimide (DCC) were purchased from Merck. Thionyl chloride (from Merck) was refluxed on linseed oil for 2 h.

Instrumental measurements Fourier transform infrared (FT-IR) spectra were recorded on a Shimadzu Model FT-IR-8101M spectrometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on FT-NMR (500 MHz) Bruker in $CDCl_3$ and DMSO-d_6. UV spectra were recorded using 2100 Shimadzu spectrophotometer. The zeta potential, static and dynamic light scattering experiments were done by a commercially available equipment Zetasizer Nano from Malvern using a 4-mW He–Ne laser (633 nm wavelength) with a fixed detector angle of 173°. The molecular weight distributions were determined by size exclusion chromatography (SEC) using 100Å column connected to a differential refractometer, refractive index (RI) and UV detector with N, N-dimethyl formamide (DMF) as the mobile phase at 25 °C. Poly(styrene) standard samples were used for calibration.

Preparation of linear–dendritic macromolecules

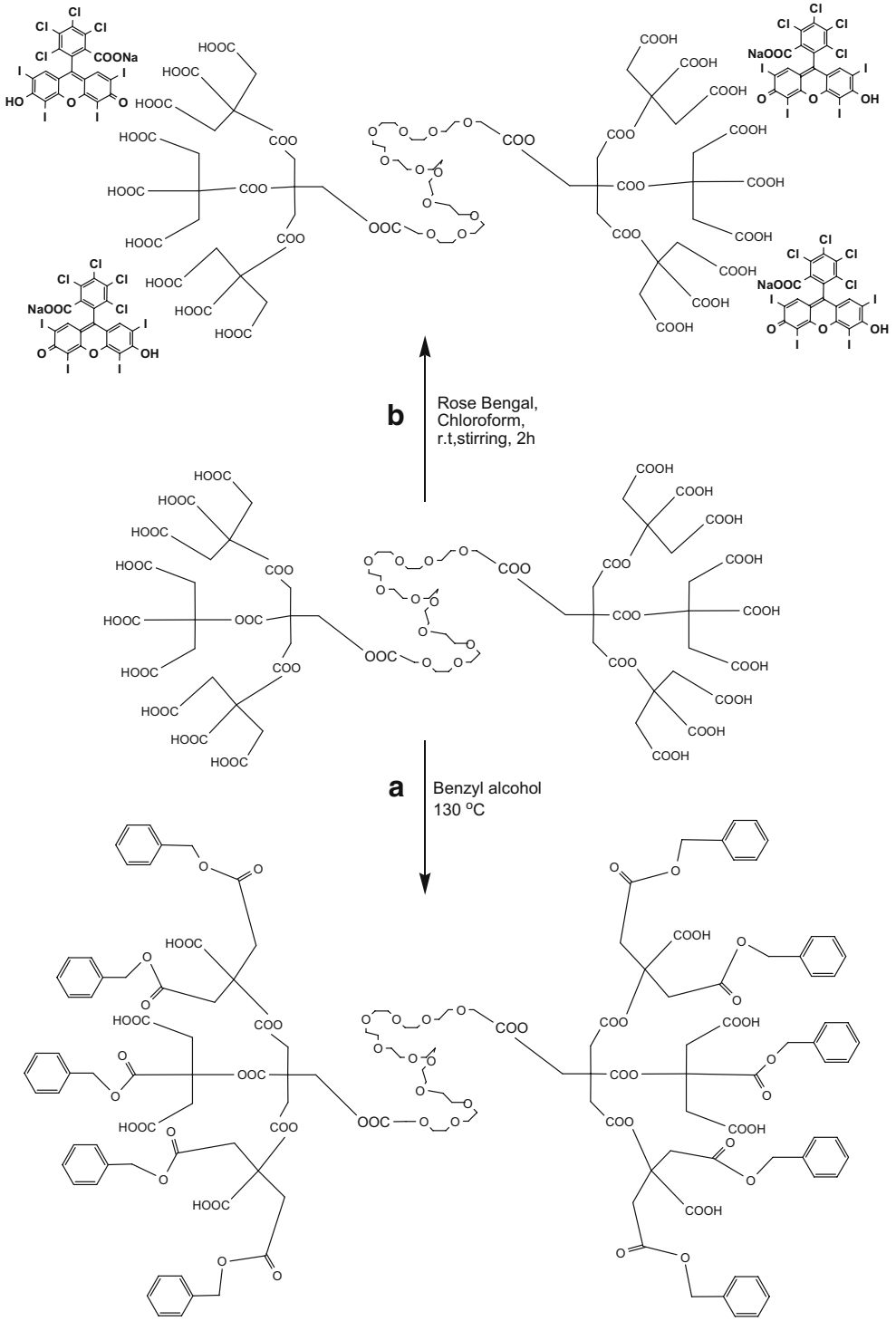
Linear–dendritic macromolecules were prepared according to the reported procedure [46]. Briefly, G_1 was prepared through reaction between poly(ethylene glycol) diacyl halide and citric acid. Reaction of G_1 with citric acid in the presence of DCC leaded to G_2. G_3 was also prepared through reaction between citric acid and activated G_2 by DCC.

General procedure for preparation of $G_{n\ (n=1-3)}$–benzyl alcohol conjugates

Different generation of linear–dendritic macromolecules (G_1, G_2, and G_3; 1.451 mmol) and benzyl alcohol (excess) were transferred into a flask equipped with vacuum inlet and magnetic stirrer. Mixture was stirred at 130 °C for 1.5 h. Water as a byproduct was removed from reaction flask using vacuum pump during the reaction. Then, mixture was dried by vacuum oven at 80 °C for 6 h. Crude product was dissolved in tetrahydrofuran (THF) and precipitated in *n*-hexane. Finally, product was added to 5 ml distilled water, and mixture was poured into a cellophane membrane dialysis bag, and it was dialyzed for 1 h. Product was dried using vacuum oven at 40 °C for 6 h. Yield for G_1, G_2, and G_3–benzyl alcohol conjugates was 68, 50, and 15%, respectively.

G_1–benzyl alcohol conjugated: ^{1}H NMR (400 MHz, δ, ppm): 7.1–7.3 (aromatic protons); 5–5.2 (benzylic protons); 3.6 [polyethylene glycol (PEG)] protons; 2.8–2.9 (citric acid protons). ^{13}C NMR (125.721 MHz, δ, ppm): 175, 172 and 171 (C=O); 139, 127, 125, and 124 (aromatic carbons); 69 and 70 (PEG carbons); 74 (benzylic carbon); 25 and 30 (citric acid carbons). Infrared (IR): 3,370 (ν_{O-H}); 3,035 and 2,780 (ν_{C-H}); 1,765 ($\nu_{C=O}$); 1,660 and 1,565 ($\nu_{C=C}$); 1,098 (ν_{C-O}) cm^{-1}. G_2–benzyl alcohol conjugated: ^{1}H NMR (400 MHz, δ, ppm): 7.2–7.3 (aromatic protons);

5–5.16 (benzylic protons); 3.6 (PEG) protons; 2.8–2.9 (citric acid protons). ^{13}C NMR (125.721 MHz, δ, ppm): 175, 172, and 171 (C=O); 139, 127, 125, and 124 (aromatic carbons); 69 and 70 (PEG carbons); 74 (benzylic carbon); 25 and 30 (citric acid carbons). IR: 3,420 (ν_{O-H}); 3,030 and 2,760 (ν_{C-H}); 1,760 ($\nu_{C=O}$); 1,660 and 1,565 ($\nu_{C=C}$); 1,090 (ν_{C-O}) cm^{-1}. G_3–benzyl alcohol conjugated: ^{1}H NMR (400 MHz, δ, ppm): 7.00–7.3 (aromatic protons); 5–5.2 (benzylic protons); 3.6 (PEG) protons; 2.8–2.9 (citric acid protons). ^{13}C NMR (125.721 MHz, δ, ppm): 175, 172, and 171 (C=O); 139, 127, 125, and 124 (aromatic carbons); 69 and 70 (PEG carbons); 74 (benzylic carbon); 25 and 30 (citric



Scheme 1 **a** Synthesis of G_2–benzyl alcohol conjugate. **b** Preparation of G_2/Rose Bengal complex

acid carbons). IR: 3,450 (ν_{O-H}); 3,020 and 2,750 (ν_{C-H}); 1,760 ($\nu_{C=O}$); 1,650 and 1,555 ($\nu_{C=C}$); 1,090 (ν_{C-O}) cm^{-1}.

Preparation of $G_{n\ (n=1-3)}$/Rose Bengal complexes

Rose Bengal (excess) was added to a chloroform solution of linear–dendritic macromolecules. Mixture was stirred for 2 h at room temperature. Then, it was filtered by microfilters, and solvent was evaporated. Crude compound was dissolved in chloroform, then it was centrifuged at 10,000 rpm for 10 min, and clear solution was decanted.

General procedures for release of guest molecules from linear–dendritic macromolecules

An amount of 30 mg of dried nanocarrier containing guest molecule was added to 5 ml of aqueous buffered solution (pH 10, 7.4, and 1) at 37 °C. Mixture was poured into a cellophane membrane dialysis bag. The bag was closed and transferred into a flask containing 20 ml of the same buffered solution maintained at 37 °C. The external buffer solution was continuously stirred, and 3 ml samples were removed at selected intervals, and 3 ml of buffer was replaced. Release was detected by UV spectrometer and determined from the calibration curve obtained previously under the same conditions.

Preparation of samples for UV experiments

A solution of nanocarrier was prepared and left at room temperature overnight; then it was filtered by microfilters. Each sample was ten times diluted and transferred to the cell of spectrophotometer. UV spectra were recorded at 25 °C, and calibration curve was used for determining the loading capacity.

Table 1 Loading capacity of G_1–, G_2–, and G_3–benzyl alcohol conjugates and G_1, G_2 and G_3/Rose Bengal complexes

Compound	Loading or binding capacity
G_1–benzyl alcohol conjugate	5
G_2–benzyl alcohol conjugate	10
G_3–benzyl alcohol conjugate	19
G_1/Rose Bengal	2
G_2/Rose Bengal	5
G_3/Rose Bengal	8

Preparation of samples for NMR experiments

A clear solution of nanocarriers was prepared, and it was transferred to the NMR tube. ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solvents on a Bruker DRX 500 (500 MHz) apparatus, with the solvent proton signal as a reference. ^{13}C-NMR spectra were recorded at 125,721 MHz on the same instrument using the solvent carbon signal as a reference. All linear–dendritic macromolecule NMR spectra were recorded on 25 mg/ml of sample.

Particle size analysis

Dynamic light scattering (DLS) experiments were performed by an equipment, Zetasizer Nano, from Malvern using a 4-mW He–Ne laser (633 nm wavelength) with a fixed detector angle of 173°. Samples were dissolved in distilled water, and measurement was performed at 25 °C and was started 10 min after the cuvette was placed in the DLS apparatus to allow the temperature to equilibrate. About 1 ml of the sample was transferred to a special dust-free light-scattering cell. The temperature was controlled to within ±0.02 °C.

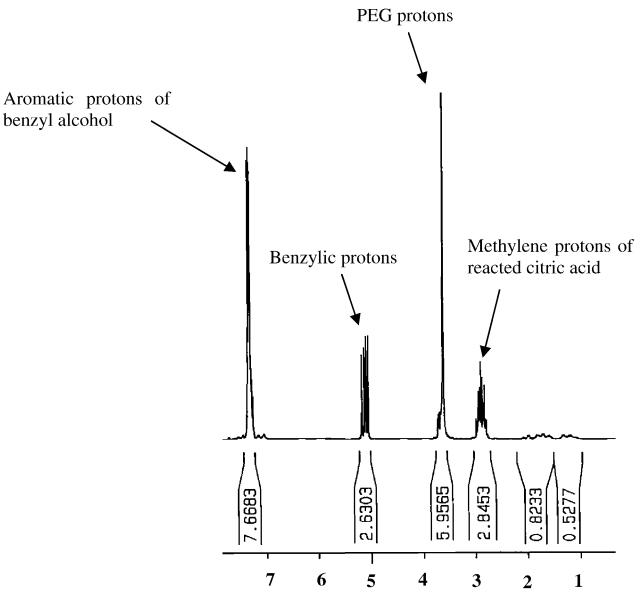


Fig. 1 ^{1}H NMR spectra of G_2–benzyl alcohol conjugate in $CDCl_3$

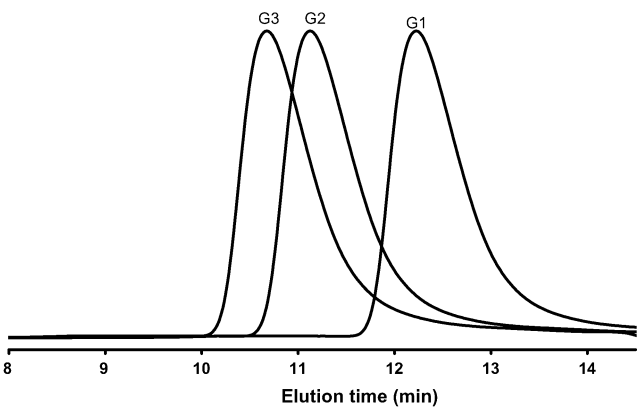


Fig. 2 GPC diagram of G_1–, G_2–, and G_3–benzyl alcohol conjugates

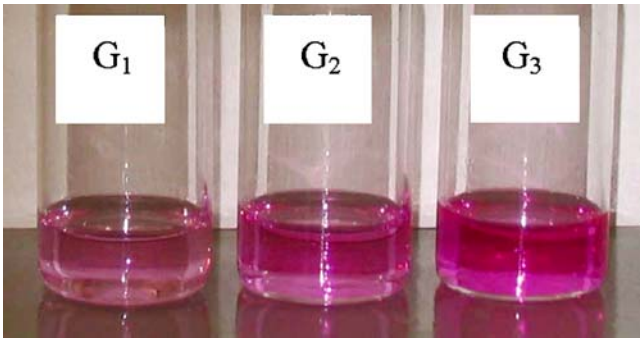


Fig. 3 Photograph of G_1, G_2, and G_3/Rose Bengal complexes in chloroform

Results and discussion

Benzyl alcohol was easily conjugated to the surface functional groups of linear–dendritic macromolecules by melting esterification reaction (Scheme 1).

Conjugation was evaluated using ^{1}H NMR experiments. Figure 1 shows ^{1}H NMR spectra of G_2–benzyl alcohol. In this figure, signals that appeared at 2.8–2.9, 3.6, 5–5.2, and 7.1–7.3 ppm are related to the CH_2 groups of citric acid, PEG, benzylic, and aromatic protons, respectively. Comparison of the ^{1}H NMR spectra of G_2 and G_2–benzyl alcohol shows that the signals of methylene groups of citric acid have shifted from 2.6–2.9 ppm (for G_2) to 2.8–2.9 ppm (for G_2–benzyl alcohol conjugate), confirming the conjugation of benzyl alcohol to the linear–dendritic macromolecule.

Loading capacity of $G_{n\ (n=1-3)}$–benzyl alcohol conjugates was calculated using ^{1}H NMR spectra. Peak area ratio of poly(ethylene glycol) or citric acid protons to benzylic protons could be used to determine the number of conjugated benzyl alcohol molecules.

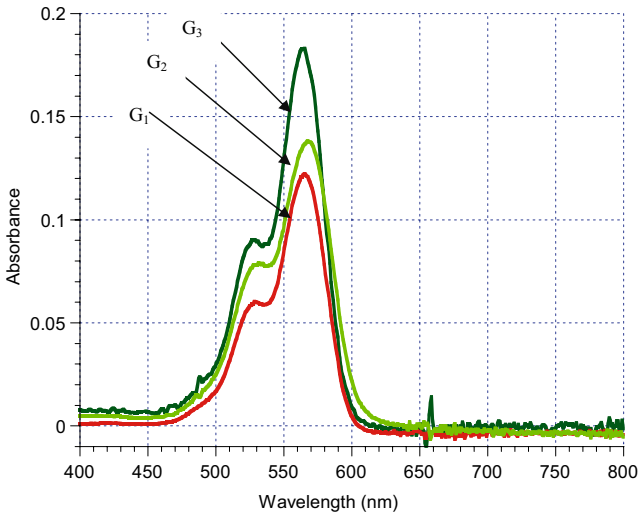


Fig. 4 UV spectra of trapped Rose Bengal by G_1, G_2, and G_3 in chloroform

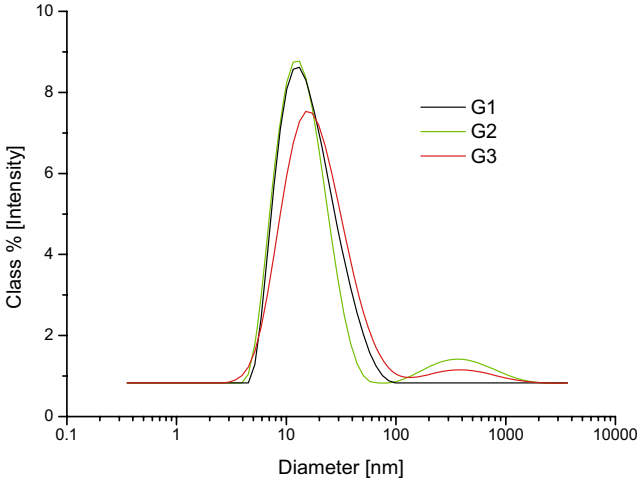


Fig. 5 Dynamic light scattering diagrams of G_1–, G_2–, and G_3–benzyl alcohol conjugates

According to ^{1}H NMR spectra, all functional groups of G_1 were reacted to benzyl alcohol; hence, conjugation efficiency of G_1 is almost equal to its functionality. Because of crowding on the surface of G_2 and G_3, some of their functional groups remained unreacted, hence their conjugation efficiency is not equal to their functionality. Table 1 shows the loading capacity of $G_{n\ (n=1-3)}$–benzyl alcohol conjugates. A direct relationship between conjugation efficiency and generation of linear–dendritic macromolecules can be seen in this table.

Although gel permeation chromatography (GPC) is not a suitable method for determination of the molecular weight of linear–dendritic macromolecules and star polymers, it can be used to compare the molecular weights of G_1–, G_2–, and G_3–benzyl alcohol conjugates. Figure 2 shows the GPC diagram of linear–dendritic conjugates. In this diagram, molecular weight is increased as generation increases.

In many cases, conjugation is not a favorable method for loading and transportation of the guest molecules. For example, when the guest molecule is not containing a suitable functional group or it is containing more than one reactive functional group or it is not stable in the conjugation condition, loading through physical interac-

Table 2 Diameter of nanocarriers obtained using DLS

Compound	Diameter (nm)
G_1–benzyl alcohol	16
G_2–benzyl alcohol	20
G_3–benzyl alcohol	45
G_1/Rose Bengal	18
G_2/Rose Bengal	38
G_3/Rose Bengal	50

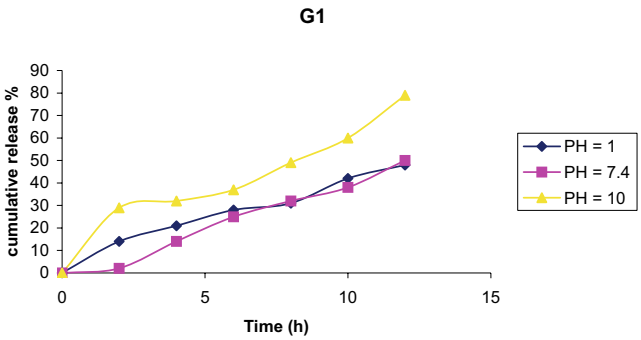


Fig. 6 Release of benzyl alcohol from G_1–benzyl alcohol conjugate, pH 1, 7.4, and 10

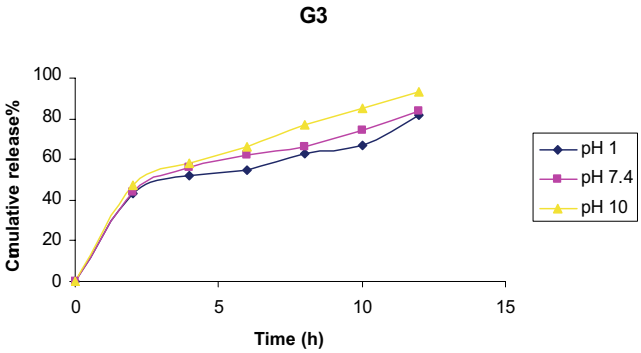


Fig. 8 Release of benzyl alcohol from G_3–benzyl alcohol conjugate, pH 1, 7.4, and 10

tions such as complexation is preferred. In this work, complexation of Rose Bengal and linear–dendritic macromolecules is investigated. Loading of Rose Bengal was carried out through addition of excess Rose Bengal to a chloroform solution of linear–dendritic macromolecules.

Loading of Rose Bengal by linear–dendritic macromolecules can be understood visually because chloroform solution of linear–dendritic macromolecules is colorless, whereas complexation changes it to red (Fig. 3). On the other hand, enhancement of intensity of red color from G_1 to G_3/Rose Bengal implies increasing of the amount of loaded Rose Bengal from G_1 to G_3.

Complexation of Rose Bengal to the linear–dendritic macromolecules was also investigated using UV experiments. Figure 4 shows the UV spectra of chloroform solution of G_1, G_2, and G_3/Rose Bengal complexes. In these spectra, λ_{max} of Rose Bengal is shifted to the higher wavelengths (bathochromic shift) of the free Rose Bengal (in water solution). Increasing the intensity of λ_{max} of trapped Rose Bengal from G_1 to G_3 shows a direct relationship between generation and amount of loaded Rose Bengal.

Loading capacity of G_1, G_2, and G_3 is given in Table 1. Again loading capacity of linear–dendritic macromolecules directly depends on generation. However, loading capacities of linear–dendritic macromolecules in this case is lower than conjugation method.

Size of nanocarriers in distilled water was investigated using DLS experiments. Diameter of G_1–, G_2–, and G_3–benzyl alcohol conjugates was 16, 20, and 45 nm, respectively (Fig. 5). Diameter of G_1, G_2, and G_3/Rose Bengal complexes was 18, 38, and 50 nm, respectively (Table 2). According to DLS experiments, diameter of complexes was bigger than conjugates.

Due to their biocompatibility and water solubility, linear–dendritic macromolecules are good candidates for drug delivery.

To study the potential application of the first, second, and third generations of linear–dendritic macromolecules as pharmaceutically potentially active compounds, the hydrolytic behavior of the conjugates and release behavior of complexes in different pH values (pH 1, 7.4, and 10 and 37 °C) was studied. Hydrolysis was carried out in cellophane membrane bags permeable to low molecular weight compounds. The released drug passed through the high molecular weight linear–dendritic macromolecules into the external buffer solution and was detected by UV spectrometer.

Figure 6 displays the release profile of conjugated benzyl alcohol from G_1, at pH 1, 7.4, and 10. In this figure, highest rate of release of benzyl alcohol from G_1 is related to pH 10 because hydrolysis of ester bond in basic medium is faster than at other pH values. Figures 7 and 8 display the release of benzyl alcohol in the same pH values from G_2– and G_3–

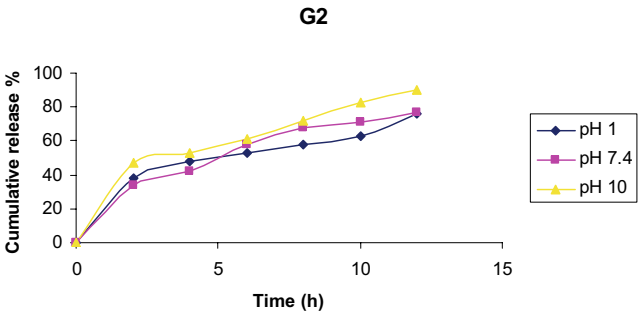


Fig. 7 Release of benzyl alcohol from G_2–benzyl alcohol conjugate, pH 1, 7.4, and 10

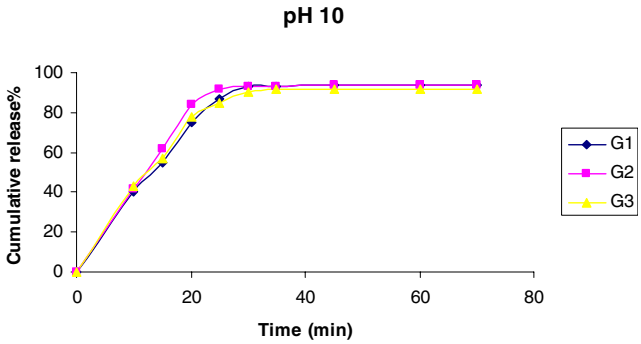


Fig. 9 Release of Rose Bengal from G_1, G_2 and G_3, and pH 10

benzyl alcohol conjugates, respectively. Again, in this paper, highest rate of release of guest molecules from linear–dendritic macromolecules is related to the pH 10. Furthermore, there is a direct relationship between generation and rate of release especially in the primary times (supporting information Figs. 1, 2, and 3).

Release of Rose Bengal from complexes was also investigated. Rate of release of Rose Bengal from linear–dendritic macromolecules was high due to weak physical interactions. In this case, release was very fast as shown in Fig. 9, and obvious differences between different pH values and generations was not detectable (supporting information Figs. 4, 5, 6, 7, 8, and 9).

Conclusion

Linear–dendritic macromolecules are able to load and entrap guest molecules by conjugation and complexation methods; hence, these systems may have potential application in transport. Because of biocompatibility and water solubility of poly(ethylene glycol) and citric acid, synthesized linear–dendritic macromolecules are good candidates for application in biological systems.

Rate of release of guest molecules from linear–dendritic macromolecules depends on several factors, such as type of interaction between host and guest molecules (physical interactions or chemical bonding), generation of linear–dendritic macromolecules, and pH.

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