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Controlled release of linear-dendritic hybrids of carbosiloxane dendrimer: The effect of hybrid's amphiphilicity on drug-incorporation; hybrid–drug interactions and hydrolytic behavior of nanocarriers

Hassan Namazi[a,b,*], Saeed Jafarirad[a]

[a] Research Labaratory of Dendrimers and Biopolymers, Faculty of Chemistry, University of Tabriz, Tabriz, Iran
[b] Research Institute for Fundamental Sciences, Tabriz, Iran

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ABSTRACT

Dendritic micelles formed from amphiphilic dendritic ABA triblock copolymers based on organic linear poly(ethylene oxide) and inorganic dendritic block containing silicon atoms (OSC–D_{Gn}–PEO–D_{Gn}–CSO, $n = 1–3$)[1] were evaluated as drug delivery vehicles for a drug in both lipophilic and hydrophilic forms. The physical parameters of the drug-incorporated carriers including the influences of drug:carrier ratio, the release kinetics of the drugs from the micellar solution were measured. The apparent partition constant of drug between the carriers and the external medium was studied as well. It was observed that the loading efficiency and hydrolytic behavior of the hybrids depend on several factors, such as type of interaction between host and guest molecules, generation of the dendritic copolymers and pH. The release profiles of the drugs from the micelle solution were found to be a slow steady release at pH 1, 7.4 and 10. Investigation of the drug release dynamics in buffered media at pH 7.4 showed that the drug released through the carriers with slight deviation follow Fickian and Case II diffusion mechanisms for drugs in lipophilic and hydrophilic forms, respectively.

1. Introduction

Among a range of micellar aggregates that have been revealed in the past century including surfactant, linear macromolecules, dendritic macromolecules, and hybrid macromolecules; the last one has fascinated great attention since its successful synthesis by Gitsov (2008). In comparison to the classical surfactant-based aggregates the linear amphiphilic macromolecules provide some distinct advantages because of their lower critical micelle concentrations and more stable aggregates than the surfactant-based micelles (Malmsten, 2002). However, linear macromolecular amphiphiles have shown several difficulties during micelle formation and in some cases micelles with ill-defined, compressed and entangled cores with broad size distribution is obtained. And these kind of mixed-self-assembled structures cause negative effects on their release behavior (Jönsson et al., 1998).

Dendritic macromolecules as the most attracting candidates offer unique merits that distinguish them from the linear macromolecules. However again, they have certain limitations. In other words an advantage that is considered to be one of their unique features could hamper the application of dendritic micelles as drug carriers. For instance, the highly ordered inner part of a dendrimer has a rigid-like effect on molecular structure of the dendrimer's interior porosities. Consequently, it limits the loading capacity of dendrimers. Thus, only the limited guest molecules with relatively small size can be entrapped even at high generations of a dendritic micelle (Jansen and Meijer, 1995).

Hybrid macromolecules as self-assembling linear-dendritic copolymers combine the advantageous properties of both linear and dendritic amphiphilic macromolecules (Gitsov, 2008; Namazi and Adeli, 2003, 2005a,b,c; Namazi et al., 2007; Didehban et al., 2009a,b, 2010). The utilization of dendritic blocks as the core forming fragments and flexible chains for the coronal loops is especially attractive since it offers a suitable system in order to form particular assemblies of highly organized entity in the center of the aggregate. In this way the micellar core will be capable of entrapping large number of molecules not only in the interior cavities of the dendritic block, but also in the space between the individual dendritic wedges (Newkome et al., 1990, 1992).

In our previous research (Namazi and Jafarirad, 2010), we reported the preparation of novel amphiphilic linear-dendritic triblock ABA type copolymers based on carbosiloaxe dendrimers.

* Corresponding author at: Research Laboratory of Dendrimers and Biopolymers, Faculty of Chemistry, University of Tabriz, Tabriz, PO Box 5166616471, Iran. Tel.: +98 4113393121; fax: +98 4113340191.
E-mail address: namazi@tabrizu.ac.ir (H. Namazi).

[1] A note on symbolism: The following example illustrates the symbolism used: OSC–DG3–PEO–DG3–CSO (G3) stand for linear-dendritic hybrids containing poly(ethylene oxide, 1000) (PEO) block as the core with third generation (DG3) of two terminal carbosiloxane (CSO) blocks, respectively to facilitate the representation of data in different sections of the manuscript.

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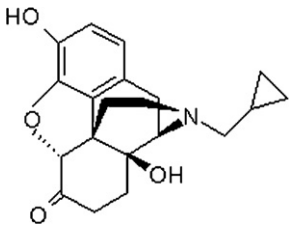

Fig. 1. Chemical structure of naltrexone.

These hybrid macromolecules have some unique advantages such as biodegradability and biocompatibility. The synthesis of silicone based delivery systems because of their potentially hydrolysable Si–O linkages have been reported (Kajihara et al., 2001). They could encapsulate guest molecules such as organic dyes (Zheng et al., 2007) and pyrene (Namazi and Jafarirad, 2010).

It should be noted that so far, very few application of these systems have been tested. We have shown that these hybrid macromolecules could self-assemble to form micellar aggregates depending on the size of the dendritic segments. On the other hand, most pathological processes exhibit a change in pH (Haag, 2004), so it has become an interesting research topic to design micellar carriers with pH-regulated releasing rate, but without loosing colloidal stability. Thus we were motivated to evaluate the release behavior of first, second and third generations (Namazi and Jafarirad, 2010) of these linear-dendritic hybrids as potential drug carriers. We selected naltrexone and its hydrochloride form as lipophilic and hydrophilic drug models, because of its probable interactions with the carrier using its different functional groups (Fig. 1). Furthermore, the release kinetics and dynamics of the drugs and the apparent partition coefficients of the drug-incorporated micelles were discussed in detail.

2. Materials and methods

2.1. Materials

Naltrexone and its hydrochloride form were gifts from Research Center for Pharmaceutical Nanotechnology (RCPN).

2.2. Methods

The hydrodynamic diameter of micellar particles was determined with a He–Ne Laser Dynamic Light Scattering (DLS) of Photon Correlation Spectroscopy-SEMATECH. A scattering angle of 90° was used for the DLS evaluations at $k = 632.8$ nm by cumulant method. Prior to size determination, all the dispersed media were filtered to remove dust particles (25–50 μm, C porosity, Ace Glass Inc., Vineland, NJ). Results corresponded to the average of three determinations. Transmission Electron Microscopy (TEM) experiments were carried out on a LEO 906 Instrument operating at an acceleration voltage of 100 kV. TEM sample was prepared by dipping a copper grid with Formvar film into the freshly prepared particle solution (0.5 mg/mL). UV–vis spectra were measured by a SHIMADZU UV-1700 Pharmaspec UV–vis Spectrophotometer, 10 mm cell, at 282 nm (pH 1 and 7.4) and 291 nm (pH 10). A solution of nanocarrier was prepared and left at room temperature overnight and then it was filtered by microfilter. Then each sample was transferred to the cell of spectrophotometer. UV–vis spectra were recorded at 25 °C and all experiments were performed at least in three replicates. Calibration curve was used for determining the drug incorporation content as well as the amount of drug release from the synthesized carriers. Dialysis tube benzoylated (Sigma–Aldrich; M_w cut-off = 1.2 kDa). The synthesis of OSC–D_{Gn}–PEO–D_{Gn}–CSO, $n = 1$–3 triblock copolymers as well as determination of critical micelle concentration (CMC) was reported in our recently published paper (Namazi and Jafarirad, 2010).

2.2.1. Encapsulation and determination of drug content in the drug-incorporated carriers

In this section the drug-incorporated carriers were prepared according to the organic solvent/water (O/w) emulsion method, the drug:carrier ratio varied from 0.1:1 to 3:1 (Table 2).

At first, the drug was dissolved in tetrahydrofuran (THF) as a water-immiscible, volatile solvent. Then, the resulting solution was poured gently into the aqueous carrier solution under vigorous agitation. This mixture was stirred for 24 h in an open air system. The drug-incorporated carrier was prepared by the evaporation of the organic solvent during the agitation (Torchilin, 2001). In order to remove free drug, the solution was purified by filtration using membrane dialysis bag and then drug-incorporated carriers in different generations were precipitated in cold n-hexane and again were dissolved in THF and reprecipitated in n-hexane for several times. The respective data for incorporation content (IC) and loading efficiency (LE) of drug-incorporated carriers are determined as follows (Eqs. (1) and (2)) and are exhibited in Table 2 (Gregory et al., 2009).

$$\mathrm{IC\,(wt\%)} = 100 \times \frac{\text{the total amount of drug in carrier}}{\text{the amount of carrier added initially}} \quad (1)$$

$$\mathrm{LE\,(\%)} = 100 \times \frac{\text{the total amount of drug in carrier}}{\text{the amount of drug added initially}} \quad (2)$$

The amount of the trapped drug into the different generations was measured with UV–vis spectrophotometery, as well as in the second procedure, the weight of the carrier before and after the incorporation was determined. Their difference is the amount of the trapped drug in the carrier.

2.2.2. In vitro release kinetics from drug-incorporated carriers

For in vitro release studies, regarding to the highest drug IC at drug:carrier ratio of 0.3–1, all samples for release investigations were prepared at the same ratio. The drug-incorporated carriers were dried in vacuum at room temperature. The drug-incorporated carriers (1 mg) were poured in 1 mL of aqueous buffered solution (pH 1, 7.4, and 10). The mixture was conducted into a cellophane membrane dialysis bag and then the bag was closed and transferred into a flask containing 10 mL of the same buffer solution and maintained at 37 °C. The bulk solution was stirred by a magnetic stirrer continuously at 800 rounds per minute (rpm) and a sample solution (0.5 mL) was withdrawn at regular selected intervals and replaced with equal volumes of the media. The quantity of the released drug was analyzed by means of UV–vis spectrophotometer and was determined by the calibration curve obtained previously under the same conditions.

2.2.3. Apparent partition constant for lipophilic drug between dendritic micelles and the outer medium

When the release of naltrexone follows a slow and linear slope, typically after 10 h at pH 7.4, 0.1 mL of the solution in the dialysis bag was placed into a centrifuge tube. The solution was centrifuged for 10 min and then the supernatant was removed carefully by pipette and transferred into a glass vial containing 3 mL of THF. The precipitate (micelles) was left in the tube and 3 mL of THF was added to it. This solution was sonicated for several minutes. The amount of the drug in all of the solutions was then determined by spectrophotometer.

2.3. Statistical data treatment

All experiments were performed at least in triplicate and the results averaged. Error bars in the figures and error values given in the tables are the calculated standard deviations.

Table 1
Physicochemical and micellar properties of the linear-dendritic hybrids in different generations (Namazi and Jafarirad, 2010), the DLS results report the mean of three replicates and error bars the standard deviation ($n = 3$).

Generation	Lipophilic block ($X_{w\%}$)[a]	M_n	cmc[b] (M) ($\times 10^{-6}$)	D[c] (nm)	μ_2/Γ^2[d]	K_v[e] ($\times 10^{-5}$)
OSC–D_{G1}–PEO–D_{G1}–CSO	32.93	1488	0.12	69 ± 1.1	0.082	0.264
OSC–D_{G2}–PEO–D_{G2}–CSO	57.20	2332	1.27	88 ± 1.5	0.099	2.77
OSC–D_{G3}–PEO–D_{G3}–CSO	76.91	4324	–	–	–	–

[a] Calculated for lipophilic carbosiloxane blocks.
[b] Measured at 25 °C.
[c] Diameter measured by dynamic light scattering in water, the data represent the mean ± SD (standard deviation), $n = 3$.
[d] Polydispersity factor.
[e] K_v, partition equilibrium constant for pyrene.

3. Results and discussion

This work consists of three sections: in the first section, drug-incorporation content (IC) and loading efficiency (LE) were optimized. In the second section, in vitro release behavior of the drug as well as evaluation on release kinetics of the drug-incorporated micelles was examined. In the last section, a comparison between apparent partition constant (K_r) and partition constant (K_v) for the synthesized linear-dendritic hybrids was investigated. Also size and size distribution of the dendritic micelles were analyzed. Recently, we reported the synthesis of different generations of new linear-dendritic amphiphilic triblock copolymers with organic/inorganic entity (see Fig. 2) (Namazi and Jafarirad, 2010).

The mean diameters of the prepared dendritic micelles were evaluated using DLS and showed 69 and 88 nm for the OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO, respectively (Table 1).

From the TEM observations the identity of the spherical micelles were demonstrated. Also TEM images showed that the OSC–D_{G1}–PEO–D_{G1}–CSO micelles were interconnected through the hydrophilic PEO blocks, resulting in a micellar network as illustrated in Fig. 3a. Concerning to OSC–D_{G2}–PEO–D_{G2}–CSO micelles, it seems that the individual flower-like structures are more appropriate structures. Therefore, we conclude that the larger carbosiloxane blocks of OSC–D_{G2}–PEO–D_{G2}–CSO relative to OSC–D_{G1}–PEO–D_{G1}–CSO counterpart have more hydrophobic interactions in the core of individual micelles (Fig. 3b). Furthermore, the short PEO blocks (M_n 1000) are not able to form bridges between two large micellar cores in micellar network. These observations are in agreement with the reported results related to the amphiphilic triblock copolymers (Booth and Attwood, 2000; Raspaud et al., 1994).

3.1. Optimization of drug IC and LE

As known, controlling the extent of LE of the micelles and subsequent release is one of the most important factors which is used in their drug delivery application assessments. Here, we aimed to control the extent of drug-IC of hybrid material with specific designing and also through the synthetic methodology. Hydrophilic/lipophilic ratio (HLR) was a key factor in the design of dendritic micelles to control the LE of the micellar systems. Therefore, the IC and LE of the drugs in all generations were analyzed in various drug:carrier weight ratios. As seen in Table 2, drug LE decreases with enhancing ratio of drug:carrier for all of generations. The maximum drug LE was obtained with drug:carrier ratios of 0.1–1.0. These results clearly pointed out that the lower drug:carrier ratios e.g., 0.1:1.0 and 0.3:1.0 cause a remarkable increase in drug IC and consequently, LE for all of the generations (Table 2). These data are comparable with literatures data in similar drug:carrier ratios (Yokoyama et al., 1998; Yu et al., 1998).

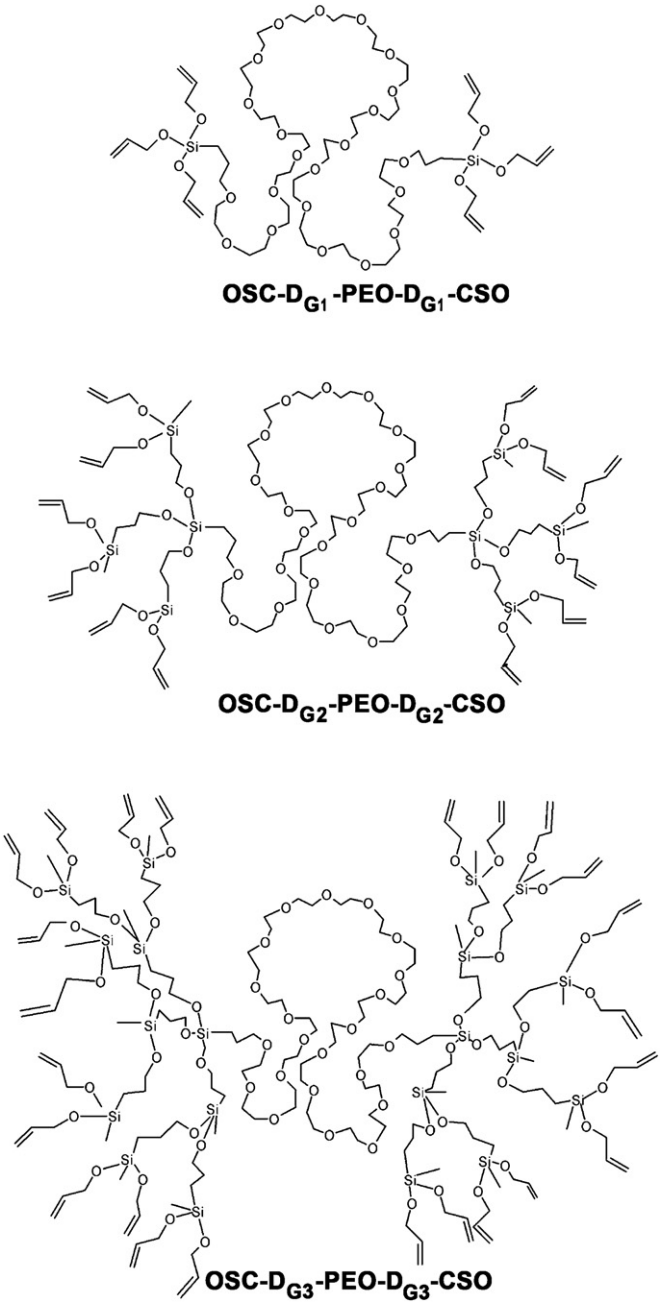

Fig. 2. Structures of the synthesized linear-dendritic hybrids in different generations; OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO and OSC–D_{G3}–PEO–D_{G3}–CSO stand for first, second and third generations, respectively.

Table 2
Effect of drug:carrier ratios on drug IC and LE in different generations, the results in the table report the mean of three replicates and error bars the standard deviation ($n = 3$).

Generation	Drug:carrier ratio (by weight)	IC[a] (LE)[b]	
		Nal. hyd.[c]	Nal.[d]
OSC–D_{G1}–PEO–D_{G1}–CSO	0.1:1.0	5.1 ± 0.4 (51.0 ± 0.7)	6.2 ± 1.0 (62.0 ± 1.6)
	0.3:1.0	5.4 ± 0.7 (18.0 ± 0.6)	6.6 ± 1.4 (22.0 ± 1.9)
	0.7:1.0	5.5 ± 0.7 (7.8 ± 0.7)	2.1 ± 0.7 (30.0 ± 1.3)
	1.0:1.0	5.9 ± 0.7 (5.9 ± 0.7)	1.6 ± 0.6 (1.6 ± 0.3)
	3.0:1.0	6.0 ± 0.9 (2.0 ± 0.4)	0.3 ± 0.1 (0.1 ± 0.0)
OSC–D_{G2}–PEO–D_{G2}–CSO	0.1:1.0	4.6 ± 0.2 (46 ± 0.6)	6.8 ± 1.1 (68.0 ± 1.7)
	0.3:1.0	4.8 ± 0.3 (16 ± 0.5)	6.9 ± 1.0 (23.0 ± 1.4)
	0.7:1.0	5.1 ± 0.5 (7.2 ± 0.5)	3.6 ± 0.5 (5.1 ± 0.4)
	1.0:1.0	5.3 ± 0.9 (5.3 ± 0.4)	2.3 ± 0.2 (2.3 ± 0.2)
	3.0:1.0	5.4 ± 1.0 (1.8 ± 0.4)	0.8 ± 0.1 (0.3 ± 0.1)
OSC–D_{G3}–PEO–D_{G3}–CSO	0.1:1.0	0.4 ± 0.1 (4.0 ± 0.3)	7.1 ± 1.5 (71.0 ± 2.5)
	0.3:1.0	0.4 ± 0.1 (1.3 ± 0.2)	7.2 ± 1.5 (24.0 ± 1.7)
	0.7:1.0	0.4 ± 0.1 (0.5 ± 0.2)	3.7 ± 0.6 (5.2 ± 0.6)
	1.0:1.0	0.5 ± 0.1 (0.5 ± 0.1)	2.3 ± 0.1 (2.3 ± 0.1)
	3.0:1.0	0.5 ± 0.1 (0.1 ± 0.0)	0.8 ± 0.1 (0.26 ± 0.1)

[a] Incorporation content (IC, wt%).
[b] Loading efficiency (LE%), the data represent the mean ± SD (standard deviation) ($n = 3$).
[c] nal. hyd.: naltrexone hydrochloride.
[d] nal.: naltrexone.

Contrarily, a large extent of precipitates was considered with drug:carrier ratios more than 1.0:1.0.

It seems that the entrapment of drugs in the carriers competes with their precipitation in the medium while their ratio increases, so it results in lowered drug IC and LE (Table 2) (Yokoyama et al., 1998). In other words, the drug molecules interact with each other more strongly than with the carriers. Thus, the drug:carrier ratio is an important factor in which significantly tunes up the drug incorporation through the drug entrapment. Our results showed a higher drug IC by using OSC–D_{G3}–PEO–D_{G3}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO, respectively. It might be justified since IC and LE for lipophilic and hydrophilic drugs are highly dependent on the weight fraction of lipophilic and hydrophilic segment in linear-dendritic hybrids as order (as illustrate in Table 1).

As shown in Table 2, the increase in the quantity of IC of entrapped naltrexone for OSC–D_{G3}–PEO–D_{G3}–CSO relative to OSC–D_{G2}–PEO–D_{G2}–CSO is lower than enhancement of IC for OSC–D_{G2}–PEO–D_{G2}–CSO relative to OSC–D_{G1}–PEO–D_{G1}–CSO. It can be due to the crowding effect as reported (Namazi and Adeli, 2005c). In the third generation the extent of porosities, to load the drug, was increased but the crowding of drug molecules is a key parameter for their loading. Consequently, in OSC–D_{G3}–PEO–D_{G3}–CSO, the crowding of drug molecules is more determinative for incorporation than the lipophilicity of the structure or the quantity of functional groups in drug molecules. Vice versa, in lower generations, the crowding is low and the polarity of the drug molecules becomes more imperative for entrapment.

3.2. Study on in vitro release behavior

In the series of hybrid macromolecules, in contrast to the fast permeation and high burst release of by OSC–D_{G3}–PEO–D_{G3}–CSO, the release by OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO was slow and no initial release burst

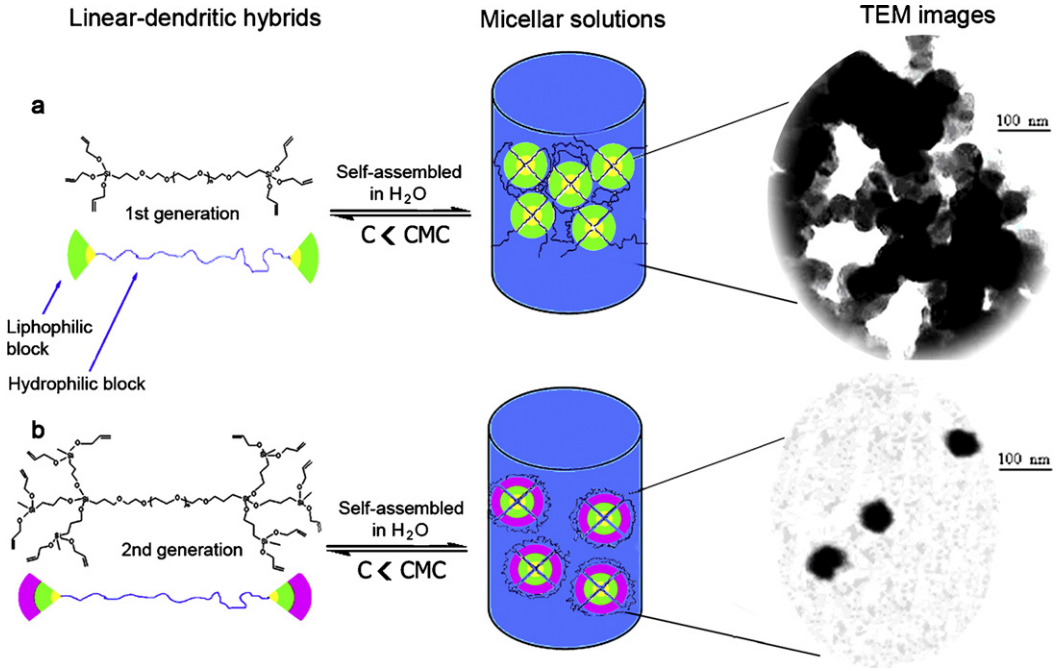

Fig. 3. A schematic describing possible structures of the dendritic micelles in aqueous medium; (a) cluster-like topology attributed to first generation and (b) flower-like topology attributed to second generation.

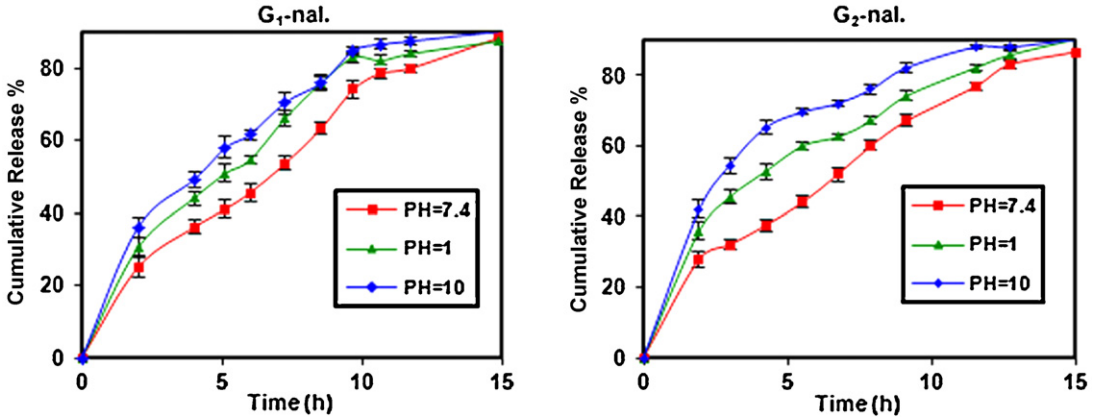

Fig. 4. In vitro release from dendritic micelles of: (a) G_1-naltrexone and (b) G_2-naltrexone as a function of time at pH 1, 7.4 and 10. Vertical error bars represent the standard deviation of the reported mean values ($n = 3$).

was observed. This phenomenon can be ascribed to the fact that OSC–D_{G3}–PEO–D_{G3}–CSO did not display micellar aggregate probably as a result of the high ratio of hydrophobic segment (Namazi and Jafarirad, 2010). Moreover, as we ultimately aimed to employ these hybrid dendrimers for in vivo applications such as injectable controlled release agents, a steady release without any burst is a vital prerequisite. Thus, we focused on the series of linear-dendritic hybrids capable to form dendritic micelles. This requirement limited our studies to the series of first and second generations. At the beginning of the drug release process, less than 28% of the loaded naltrexone showed a burst release during the first 1 h for OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO dendritic micelles. It might be as a result of the diffusion of the drug that was poorly encapsulated in the corona part of the micelles. After the burst release, a sustained release of the loaded lipophilic drug continued. This controlled release for the carriers is a major result of hydrophobic interactions of the drug and the lipophilic core of the carriers. Remarkably, drug release from OSC–D_{G2}–PEO–D_{G2}–CSO micelles (Fig. 4) was slower than from OSC–D_{G1}–PEO–D_{G1}–CSO ones. The obtained release profile might be attributed to the higher drug IC in OSC–D_{G2}–PEO–D_{G2}–CSO micelles (0.3:1, 6.9 wt%) relative to drug IC in OSC–D_{G1}–PEO–D_{G1}–CSO micelles (0.3:1, 6.6 wt%). The higher drug IC in the series of dendritic micelles was believed to enhance interactions between the lipophilic drug and the lipophilic segments of the linear-dendritic hybrids, which reduces the release rate (Chakraborty et al., 2003).

On the other hand, as seen, the highest rate in the release profiles is related to pH 10. In general, the release rate at pH 1 is higher than pH 7.4 and lower than the pH 10. The observed results could be related to the relative stability of the carriers in the above different pHs.

Furthermore, the hydrolytic behaviors of the OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO micelles loaded with naltrexone hydrochloride showed a release profile similar to that of the hydropholic drug (Fig. 5). However, its release was approximately faster than lipophilic one having further burst release.

It can be assigned to the fact that hydrophilic drug was incorporated mostly into the exterior hydrophilic segment of the micelles, conversely to lipophilic one, which results to easier diffusion than the lipophilic drug. Consequently, at first, the hydrophilic drug in the exterior hydrophilic shell starts to release with a fast rate and then some of hydrophilic drugs which were loaded in the inner core of the carriers released in a steady way. The incorporation of hydrophilic drug in the core of the dendritic micelles possibly could be as a result of negative electronic entity of the core of the micelles containing functional CH_2=CH double bonds which tend to attract hydrophilic drug. Based on reports (Cai et al., 2006), CH_2=CH bonds can influence negative surface charge to some extent while in the hydrophilic drug, somewhat positive surface charge is present. It can be due to the presence of ammonium hydrochloride salt (Shiraishi et al., 2009). Although, increasing the amount of double bonds in OSC–D_{G2}–PEO–D_{G2}–CSO than OSC–D_{G1}–PEO–D_{G1}–CSO, did not result to more IC of hydrophilic drug implying that the most of hydrophilic drug entrapped into the exterior part of the carriers.

3.3. Evaluation on release kinetics

To analyze the mechanism of the release of the drugs from the carriers, the release kinetic parameters were calculated using the Eq. (3):

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t/M_∞ is the fraction of drug that has been released by time t, k is a kinetic constant and n is the release exponent which is

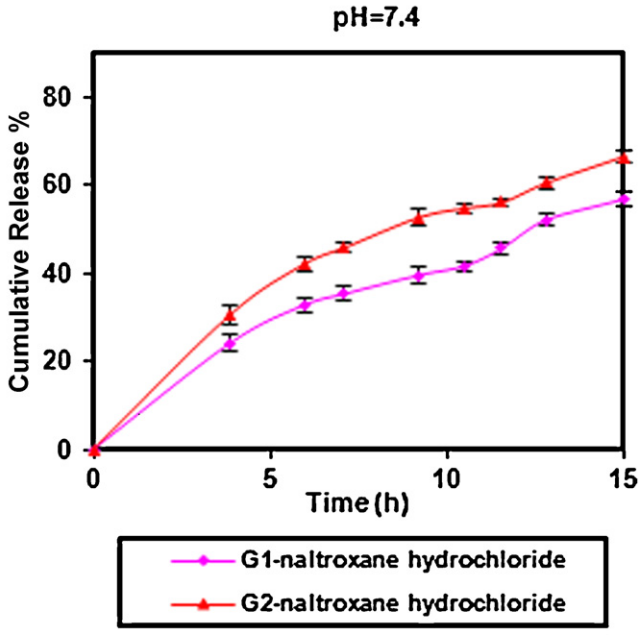

Fig. 5. In vitro naltrexone hydrochloride release from OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO dendritic micelles as a function of time at pH 7.4. Vertical error bars represent the standard deviation of the reported mean values ($n = 3$).

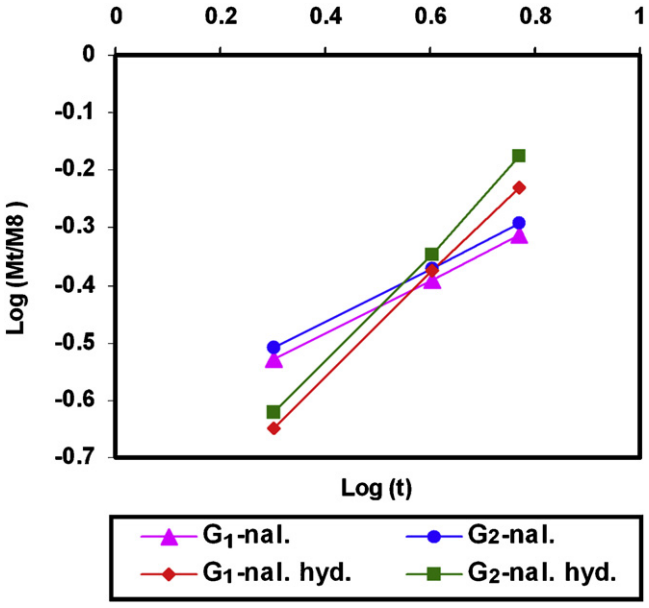

Fig. 6. Profiles of Log (M_t/M_∞) versus Log t in case of all the drug-incorporated carriers at pH 7.4.

indicative of the release mechanism. As k increases, the release of the drug occurs more quickly. For Normal Fickian diffusion, Case II diffusion and Non-Fickian diffusion the values of n are 0.5, 1.0 and 0.5–1.0, respectively (Ritger and Peppas, 1987). Eq. (3) can be converted to linear form as Eq. (4):

$$\text{Log}\left(\frac{M_t}{M_\infty}\right) = \log k + n \log t \tag{4}$$

The fitting results using the above model are indicated in Fig. 6.

The values n, k and R^2 have been evaluated for the release studies of all drug-incorporated carriers from the Fig. 6 and the obtained results are summarized in Table 3.

In general, only the data respective to the first 60% of the released drug at pH 7.4 have been employed in mathematical evaluations. Experimental data were analyzed by nonlinear least-squares regression. The values of k are between 0.101 and 0.273. Drug release from all carrier systems has satisfactory fitness with Eq. (4). R^2 has greater value than 0.99 except G_2-naltrexone. In all cases, n as the release exponent for the carriers lies between 0.497 (G_1-naltrexone) and 1.061 (G_2-naltrexone hydrochloride), suggesting diffusion-controlled release (Table 3).

It must be noted that the drug-incorporated carriers in this work are not swellable in contact with solution medium. In such situations the threshold of n value between Fickian and non-Fickian mechanism must be supposed 0.45 instead of 0.5 (Gu et al., 2007). Thus, diffusion process related to the lipophilic drug-loaded carriers has a good agreement by Fickian mechanism. As seen, the LE of the loaded lipophilic drug (with drug:carrier ratio of 0.1–1) was decreased through order of G_2-naltrexone > G_1-naltrexone (Table 2). On the other hand, R^2 values in Table 3 shows that deviation is clearly related to the LE of the loaded drug. Regarding to the data in Tables 2 and 3, it is revealed that G_1-naltrexone has fewer LE than G_2-naltrexone and thus less deviation from the Fickian mechanism. This trend is observed about the hydrophilic drug-incorporated carries too. For example, G_2-naltrexone hydrochloride has less deviation from the Case II diffusion mechanism. And similarly, LE of the loaded drug molecules (with ratios of 0.1:1.0) is diminished through order of G_1-naltrexone hydrochloride > G_2-naltrexone hydrochloride (Table 2).

Table 3
The calculated values of n, k and R^2 for the drug- incorporated linear-dendritic hybrids.

Drug-incorporated carriers	Parameter		
	n	k	R^2
G1-nal.[a]	0.497 ± 0.069	0.273 ± 0.003	0.998
G2-nal.	0.486 ± 0.069	0.232 ± 0.015	0.996
G1-nal. hyd.[b]	0.985 ± 0.054	0.114 ± 0.003	0.994
G2-nal. hyd.	1.061 ± 0.051	0.101 ± 0.002	0.999

[a] nal.: naltrexone.
[b] nal. hyd.: naltrexone hydrochloride; the data represent the measured values of mean ± SD (standard deviation) (n = 3).

3.4. Apparent partition constant for naltrexone between the micelles and the external medium

In order to apply the dendritic micelles as potential carriers, it is vital to determine the hydrophobicity of the micelles. K_v, partition equilibrium constant, for model lipophilic compounds (pyrene) between the dendritic micelles and the external medium has been described in detail elsewhere (Namazi and Jafarirad, 2010). In this case, the apparent partition constant (K_r) must be used instead of the partition constant (K_v). It is due to the fact that the measurement of the amount of the drug in the micelles and the external medium has been affected by the dialysis process. Thus, the partitioning of the drug will be a sign of the amount lost during the dialysis process by burst release. The theoretical model to investigate this process could be summarized as Eq. (5):

$$\frac{[\text{Drug}]_{\text{miscelles}}}{[\text{Drug}]_{\text{water}}} = \frac{K_r C X_w}{\rho} \tag{5}$$

where $[\text{Drug}]_{\text{micelles}}$ is the concentration of drug in the micelles (precipitate following centrifugation), $[\text{Drug}]_{\text{water}}$ is the concentration of drug in the external medium (supernatant following centrifugation), C is the dendrimer concentration, X_w is the weight fraction of hydrophobic blocks in the copolymer, and ρ is the density of hydrophobic block in the micelles. The value of K_r of first and second generations were found 0.017×10^5 and 0.103×10^5 for naltrexone, respectively, suggesting that the drug was favored to stay in the hydrophobic part of the dendritic micelles. On the other hand, with increasing generation of hydrophobic dendritic block, K_r increases as well. These values for K_r are comparable with those of linear diblock copolymers micelles such as PCL_{20}-b-PEO_{44} (0.19×10^5) in which PCL and PEO stand for polycaprolactone and poly (ethylene oxide) (Allen et al., 2000). It should be reminded that as expected, the K_r of the drugs are less than $K_{v,\text{pyrene}}$ (0.264×10^5 and 2.77×10^5 for OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO, Table 1), confirming the burst release of the drug at the hydrolytic circumstances. This comparison could serve as a favorable preliminary evaluation of the applicability of linear-dendritic hybrids as drug carriers.

3.5. Size and size distribution of the loaded micelles

The mean diameters of the micelles, measured by dynamic light scattering, were 69 and 88 nm for OSC–D_{G1}–PEO–D_{G1}–CSO and OSC–D_{G2}–PEO–D_{G2}–CSO micelles (Namazi and Jafarirad, 2010), respectively suggesting that the hydrophobic dendritic block of a higher generation induced larger micelles. In order to obtain long blood circulation half-lives, nanocarriers must be small enough and a drug delivery system with size smaller than 200 nm is desired for a long-circulating drug carrier (Kabanov et al., 2002). After loading naltrexone, as a typical example, the diameter of carriers using DLS experiments was determined to be 97.7 and 136.7 nm for the first and second generations, respectively.

4. Conclusions

In the present work a series of drug-incorporated dendritic micelles from the synthesized linear-dendritc hybrids have been developed. In order to load drugs into the micelles, the drug:carrier ratio appreciably tuned up drug incorporation content and loading efficiency. For all the studied linear-dendritic hybrids, the highest drug loading efficiencies were achieved with a 0.1:1 drug:carrier ratio. Overall, the results from this study highlight the potential of the newly synthesized linear-dendritic hybrids based on carbosiloxane chemistry. Based on our experience, OSC–D_{G2}–PEO–D_{G2}–CSO represents better potential for sustained release of lipophilic and hydrophilic drugs than OSC–D_{G1}–PEO–D_{G1}–CSO one. Also, the obtained results demonstrate that the release profiles are in agreement with Fickian and Case II diffusion-controlled mechanism. It is speculated that the presence of PEO and absence of cationic groups at the surface could inject some advantages on biomedical application such as enhancing biocompatibility and reducing cytotoxicity into the prepared delivery vehicles.

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