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Novel linear–globular thermoreversible hydrogel ABA type copolymers from dendritic citric acid as the A blocks and poly(ethyleneglycol) as the B block

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Abstract

The syntheses of novel linear–dendritic thermoreversible hydrogel copolymers were achieved via two procedures. In the first procedure synthesis of linear–dendritic copolymers carried out through an esterification step using thionylchloride and pyridine. In the second procedure linear–dendritic copolymers were prepared using dicyclohexylcarbodiimide and pyridine. The citric acid as the monomer unit was used for the preparation of ester-linked fragments. Diacid poly(ethyleneglycol) was chlorinated and diacyl halide poly(ethyleneglycol) prepared and used as the core. The formation of water soluble inclusion complexes with a variety of small size guest molecules is also described. Moreover, the thermoreversible behavior of the prepared hydrogels of both citric acid–poly(ethyleneglycol)–citric acid (CA–PEG–CA) triblock copolymers and the complexes derived from CA–PEG–CA triblock copolymers with various drugs have been investigated. The structure definition and analysis of the new resulted triblock copolymers and their complexes were carried out using NMR, optical microscopy, viscosimetry, FT–IR and UV–VIS spectrometry methods.

Keywords: Citric acid; Linear–dendritic; Biodegradable; Poly(ethyleneglycol); Dendritic thermoreversible hydrogels

1. Introduction

Polymers and copolymers having complex and well-defined structures (stars, rings, dendrimers, ladders, etc.) are drawing increasing attention to the search for the new materials with unconventional or improved properties [1]. Hybrid copolymers consisting of flexible and rigid segments are particularly interesting because of their various potential applications from drug delivery systems to compatibilizing agents, thickeners, etc. [2]. The preparation of highly defined dendritic macromolecules by the convergent growth or the starburst (divergent growth) approaches has been well documented [3–7]. These dendritic macromolecules have a unique architecture, which is characterized by a high degree of branching that originates from a central point at each monomer unit, and a large number of chain ends or surface functional groups. Due to these factors, the globular and three-dimensional structures are obtained which possess new and unusual characteristics such as the absence of the classical entanglements found in linear polymers and a bell-shaped relationship between viscosity and molecular weight [8]. These combined abilities permit the synthesis of the novel dendritic block copolymers, which extend further the increasingly important fields of both dendritic macromolecules and block copolymers. The synthesis of hybrid macromolecules containing dendrimers have been reported by several research groups [9–11]. Fréchet et al. developed methods for the synthesis of novel hybrid copolymers with linear–globular architecture. They were obtained for the first time as the amphiphilic hybrid copolymers containing both flexible and semi-rigid blocks, using the preformed

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poly(ethyleneglycol)s and polyethylene oxide(s) as the linear component and aromatic dendritic polyethers as the globular component [12,13]. Also important contributions to this field have been the synthesis of structures containing dendrimers and linear macromolecules [14]. Fréchet's dendritic linear block copolymers [15], Chapman's hydraamphiphiles [16] and the amphiphilic polymers as described by Zhong and Eisenberg [17] already showed the versatility of the introduction of dendrimers into amphiphilic molecules. They can be regarded as the intermediates between solids and liquids, which manifests in a rather complex mixture of the properties of these limiting states. In the recent years, thermosensitive systems and hydrogels have attracted much attention [18], because the viscoelastic characteristics can be easily controlled by changing the temperature. Also temperature-dependent physical gelation of synthetic polymers has been extensively studied during the last two decades. The interest to these thermoreversible polymers arising from their promise for different applications [19]. Three general thermoreversible gelation mechanisms are reported in the literature [20]: solvent-induced gelation, crystallization-induced gelation and micellar gelation. A typical example of the last case, micellar gelation is an aqueous solution of poly(ethylene oxide)/poly(butylenes oxide) or poly(ethylene oxide)/poly(propylene oxide) block copolymer such as commercial Pluronics (BASF), which shows a thermoreversible sol–gel transition dependent on temperature, and can be developed for various applications such as polymeric drug carriers, implantation and other medical applications [21]. These structure-designed di- or triblock copolymers, when they are above the critical gel concentration, form micelles in water at low temperature and induce gelation with increasing temperature because of micelle aggregation or packing. However, most of the synthetic polymers mentioned above are non-biodegradable, and induce toxicity in the body. For example, Pluronics have been found to induce toxic enhancement of plasma cholesterol and triglycerol after intraperitional infection because they are non-biodegradable and gradually accumulated in the body [22]. Therefore, the biodegradable block copolymers composed of PEG and biodegradable polyester, such as poly(L-lactic acid) (PLLA), poly(D- and L-lactic acid) (PDLA), poly(lactic acid-co-glycolic acid) (PLGA) and poly(D, L-lactic acid-co-ε-caprolactone) (PDLA-co-PCL), have received special attention in the recent years, because they could be applied as medicine in implantation and wound treatment, or as controlled-release drug carriers. Also many researchers have reported the synthesis of multiblock copolymers of PEG–polyester in recent years [23]. Li and co-workers [24] reported the synthesis of poly(ethyleneglycol)–poly(caprolactone) (PEG–PCL) multiblock copolymers with high molecular weight (above 20,000) by the polycondensation of PEG bearing two carboxylic end groups and PCL diols in the presence of dicyclohexylcarbodiimide (DCC) as a condensing agent. They have pointed out that these multiblock copolymers degraded in a biotic hydrolytic way. Investigation of the thermoreversible properties of PEG–PCL multiblock copolymers has been reported [25]. Yuh and Bae [26] synthesized the PEG/PLLA alternating multiblock copolymer by multistep condensation polymerization of PEG and PLLA in the presence of DCC and N,N-dimethylamino pyridine, and found that microcrystalline domains of PLLA formed in the hydrogel.

In this work we report the synthesis of thermoreversible hydrogel triblock copolymers (CA–PEG–CA) through two procedures. In the first procedure the synthesis of linear–dendritic copolymers carried out through an esterification step using thionylchloride and pyridine. In the second procedure linear–dendritic copolymers was prepared using DCC and pyridine. The host-guest behaviour for some guest molecules and drugs was studied. The structure and also thermoreversible hydrogel properties of the first generation (G_1), the second generation (G_2) of dendritic copolymers and drug/dendrimer complexes were investigated using ^{1}H NMR, FT–IR, UV–VIS spectrometry, viscosimetry and optical microscopy methods.

2. Experimental

Poly(ethyleneglycol) 600 diacid (acid number 175, 96–98%, from Fluka) was dried over Na_2SO_4. Citric acid, 5,7-dibromo-8-hydroxy quinoline and pyridine (purified with refluxing over NaOH for 2 h and subsequent distillation) were obtained from Merck. Thionylchloride (from Merck) was purified by refluxing a mixture of 10 wt.% linseed oil in thionylchloride for 2 h and subsequent distillation. DCC purchased from Merck. 5-Amino salicylic acid (5-ASA) was purchased from Aldrich and recrystallized from water.

Instrumental measurements: FT–IR spectra were measured on a Shimadzu Model FT–IR-8101M spectrometer. ^{1}H NMR spectra were recorded on FT–NMR (200 MHz) Brucker in DMSO-d_6, acetone deuterium and acetone in the presence of DMSO. For the investigation of bis-globular/drug complex compounds UV 2100 Shimadzu spectrophotometer was applied. The optical microscopy was performed using a Nikon microscope equipped with Nomarsky optics.

2.1. Preparation of α,ω-di(chlorocarbonylmethylene) poly(ethyleneglycol) (PEG–COCl)

The diacyl halide poly(ethyleneglycol) was prepared by literature method [27]. In this procedure, dry poly(ethyleneglycol) 600 diacid (PEG-A) was chlorinated

with refluxing in thionylchloride and ClOC–PEG–COCl obtained as the light yellow oil, yield 100%.

2.2. Preparation of G_1 using thionylchloride

A solution of citric acid (0.637 g, $1.66 \times 10^{-3} \times 2$ mol) in 20 ml dry (DMF) was placed in a round-bottom flask equipped with a reflux condenser, dropping funnel, argon inlet and magnetic stirrer. Dry pyridine (0.2 ml, 2.48×10^{-3} mol) was added to this solution at 15 min through dropping funnel and mixture was stirred for 20 min. A solution of ClOC–PEG–COCl (1.057 g, 1.66×10^{-3} mol) in 10 ml dry DMF was added at 0 °C for 30 min. The mixture was stirred at 0 °C for 1 h then at room temperature for 3 h and finally at 50 °C for additional 6 h (all steps of reaction was carried out under argon) then was cooled and filtered off and was precipitated in diethylether. The product was washed using dichloromethane, cooled acetone, toluene and dissolved in 10 ml DMF and reprecipitated in diethylether and *n*-hexane for several times. The mixture was poured in 5 ml of water at 25 °C. The mixture was conducted into cellophane membrane dialysis bag. The bag was closed and transferred into a flask containing 100 ml of water maintained at 25 °C. The external water was continuously stirred for two days. The external water was removed after 24 h and added 100 ml fresh water, then the product was removed from dialysis bag and dried under vacuum at 50 °C as the reddish oil, yield 70%.

2.3. Chlorination of G_1

A mixture of compound G_1 (0.5 g, 5.27×10^{-4} mol) and dry pyridine (0.3 ml, 3.72×10^{-3} mol) was placed in a round-bottom flask equipped with a reflux condenser, dropping funnel, argon inlet and magnetic stirrer. A very purified thionylchloride (20 ml) was added to the mixture at 0 °C for 30 min. The mixture was stirred at 0 °C for 1 h then refluxed for additional 16 h. The mixture was cooled and filtered off and the excess of thionylchloride was distilled under vacuum at 40 °C. Then 2×10 ml dry dichloromethane was added to the solution, and the solvent was evaporated under vacuum to remove the traces of thionylchloride and finally the target compound was obtained as the oil yield 80%.

2.4. Preparation of G_2 using thionylchloride

A solution of citric acid (1 g, 5.2×10^{-3} mol) in 20 ml of dry DMF was placed in a round-bottom flask equipped with a reflux condenser, dropping funnel, argon inlet and magnetic stirrer. Dry pyridine (0.4 ml, 5.2×10^{-3} mol) was added to this solution using dropping funnel (15 min) and the mixture was stirred for 20 min by vigorous stirring. A solution of chlorinated G_1 (0.91 g, 8.66×10^{-4} mol) in 10 ml dry DMF was added to this mixture by funnel dropping at 0 °C for 1 h. The mixture was stirred under argon at 0 °C for 2 h then at room temperature for 5 h and finally at 50 °C for 10 h. Then the mixture was cooled, filtered off and precipitated in diethylether. The product was washed by dichloromethane, cool acetone and toluene. The product was dissolved in DMF and reprecipitated in diethylether and *n*-hexane for several times. The mixture was poured in 5 ml water at 25 °C and was conducted into cellophane membrane dialysis bag. The bag was closed and transferred into a flask containing 100 ml of water maintained at 25 °C. The external water was continuously stirred for two days. The external water was removed after 24 h and added 100 ml fresh water. The product was removed from dialysis bag and dried under vacuum at 50 °C as the amorphous compound, yield 40%.

2.5. Preparation of G_2 using dicyclohexylcarbodiimide

A solution of G_1 (2 g, 2.1×10^{-3} mol) in 15 ml dry DMF was added to a round-bottom flask equipped with reflux condenser, argon inlet, dropping funnel and magnetic stirrer. Dry pyridine (0.2 ml) was added to this solution by dropping funnel (15 min). The mixture was stirred vigorously for 10 min. A solution of DCC (0.52 g, 2.52×10^{-3} mol) in 10 ml dry DMF was added to mixture at 0 °C by dropping funnel. The mixture was stirred for 20 min. Then a solution of citric acid (0.483 g, 2.52×10^{-3} mol) in 10 ml DMF was added dropwise to this solution. The mixture was stirred at 0 °C for 1 h then at room temperature for 24 h under argon. The solution was filtered off and was placed at 5 °C for 24 h and again the solution was filtered off. The product was precipitated in diethylether and was washed by acetone dichloromethane, toluene then dissolved in DMF and reprecipitated in diethylether for several times. The product was dissolved in 5 ml water and stirred for 24 h at room temperature. The solution was filtered off and poured in 5 ml of water at 25 °C. The mixture was conducted into cellophane membrane dialysis bag. The bag was closed and transferred into a flask containing 100 ml of water maintained at 25 °C. The external water was continuously stirred for two days. The external water was removed after 24 h and added 100 ml fresh water. The product was removed from dialysis bag and dried under vacuum at 50 °C as the amorphous compound, yield 50%.

2.6. Preparation of G_3 using DCC

A solution of G_2 (2 g, 1×10^{-3} mol) in 15 ml dry DMF was added to a round-bottom flask equipped with reflux condenser, argon inlet, dropping funnel and magnetic stirrer. Dry pyridine (0.2 ml) was added to this solution by dropping funnel at 15 min. The mixture was stirred vigorously for 20 min. A solution of DCC (0.309

g, 1.5×10^{-3} mol) in 10 ml of dry DMF was added to mixture at 0 °C by dropping funnel. The mixture was stirred for 20 min. Then a solution of citric acid (0.288 g, 1.5×10^{-3} mol) in 10 ml of DMF was added dropwise to this solution. The mixture was stirred at 0 °C for 1.5 h then for additional 72 h under argon at room temperature. The solution was filtered off and placed at 5 °C for 24 h and again the solution was filtered off. The product was precipitated in diethylether and washed by acetone, dichloromethane (for removing the excess of citric acid), and toluene then dissolved in DMF and reprecipitated in diethylether for several times. The product was dissolved in 5 ml water and stirred for 24 h at room temperature. The solution was filtered off and poured in 5 ml of water at 25 °C. The mixture was conducted into cellophane membrane dialysis bag. The bag was closed and transferred into a flask containing 100 ml of water maintained at 25 °C. The external water was continuously stirred for two days. The external water was removed after 24 h and added 100 ml fresh water. The product was removed from dialysis bag and dried under vacuum at 50 °C as the solid, yield 10%.

2.7. Preparation of the complex of G_3 and pyridine

For the complex formation first G_3 was dissolved and stirred in pyridine for 2 h, then the product was precipitated in diethylether. The obtained product was dissolved in water or ethanol/water (1:4, v/v) at 80 °C and stirred for 0.5 h then filtered off and water was removed under vacuum at 80 °C. The complex was dissolved in methanol, filtered and was precipitated in diethylether and washed by acetone, diethylether and toluene to yield the yellow solid compound.

2.8. Preparation of complex of G_1 and 5,7-dibromo-8-hydroxy quinoline

A solution of G_1 in 20 ml THF was added to a round-bottom flask equipped with reflux condenser and magnetic stirrer. Excess of 5,7-dibromo-8-hydroxy quinoline was added to the solution and was stirred for 2 h at 30 °C. Then the complex was precipitated in *n*-hexane and then was dissolved in dichloromethane and reprecipitated in diethylether for several times to yield the green oil compound.

2.9. Preparation the complex of G_1 and 5-aminosalicylic acid

A solution of G_1 in 20 ml ethanol/DMF (3:1, v/v) was added to a round-bottom flask equipped with a reflux condenser and magnetic stirrer. Excess of 5-ASA was added to the solution and the solution was stirred for 2 h at 30 °C. Then the complex was precipitated in diethylether and was dissolved in dichloromethane and reprecipitated in diethylether for several times to yield the red–brown oil compound.

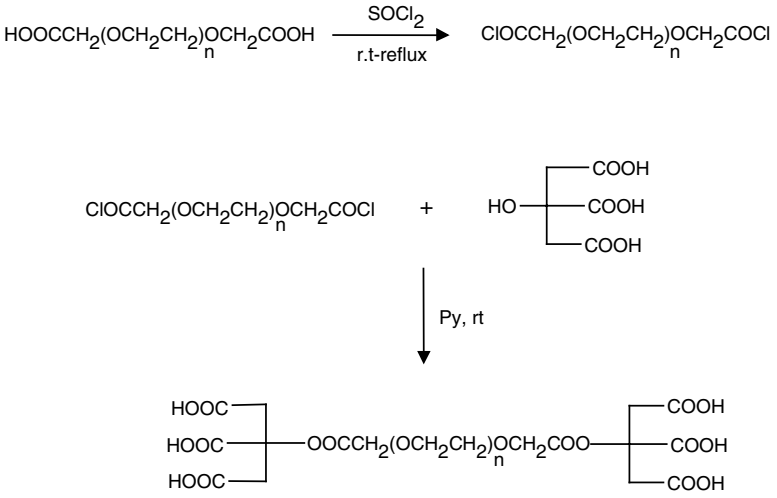
2.10. Preparation of bis-globular and drug/dendrimer complex gels

The 2%, 4%, 6% and 8% (w/v) solutions of the bis-globular and drug/dendrimer complexes in hot water and hot ethanol/water was prepared and filtered to exclude dust particles. When these solutions were cooled below the transition temperature they become opaque with the formation of gels. Viscosity measurements indicated a gelation temperature in the interval of 45–67 °C. Some hysterisis was observed when cycling over the transition temperature.

For the microscopy studies the gels were diluted 10 times with the above mixed solvent. For the optical microscopy the films were prepared by smearing a few drops over a glass slide and air drying for 60 min.

3. Results and discussion

The compound G_1 was synthesized from the reaction of ClOC–PEG–COCl with anhydrous citric acid (Scheme 1) and ClOC–PEG–COCl was prepared through chlorination of diacid poly(ethyleneglycol) using thionylchloride in yield 100%. In Fig. 1(a) the ^{1}H NMR of G_1 which shows a quartet at 2.6–2.9 ppm as a AB system for the CH_2 protons of citric acid [28], the protons of PEG at 3.6–3.9 ppm (–OCH_2CH_2O–) and 4.1–4.2 ppm (–$COCH_2O$–) can be recognized also the chemical shifts at 2.5 ppm is related to the DMSO as the solvent. The integral ratio of aliphatic protons of PEG to the citric acid part of the molecule is 6 (in comparison to 6 as a theoretical calculation). This is an evidence, which shows the reaction has been accomplished completely and both of the acyl halide functions of chlorinated poly(ethyleneglycol) have been reacted with citric acid. Although water is one of the best solvents of PEG and citric acid however, G_1 is not soluble in this solvent at room temperature. When the G_1 was placed in water, an opaque mixture was formed which could be related to the aggregation of G_1 molecules. Up to several weight percent (5% wt.) of G_1 was dissolved in some of the hot solvents such as ethanol/water (1:4, v/v) and DMF/water. On cooling of the above solutions they became opaque again with gel formation. The thermally reversible gels were prepared and studied by viscometry, optical microscopy and NMR spectroscopy by usual methods [29]. We use the viscosity measurements for determination of transition temperature (sol to gel) by using a Wells–Brookfield cone and plate steady share viscometer (model LVDP). The viscosity of ethanol/water solution (1:4, v/v) of this compound was measured during gelation. A 4.0 wt.% of G_1 solution in ethanol/



Scheme 1. Synthesis of G_1.

water (1:4, v/v) was prepared at 80 °C, transferred to a viscometer at 25 °C and the viscosity was measured as the solution when it was gelated. At the onset of gelation (40–45 °C) the viscosity increased as the solution begins to be opaque. Hence the transition temperature of G_1 was 40–45 °C. Phase-transition temperature (gel to solution) for ethanol/water solution (1:4, v/v) of G_1 was determined using viscometry and the results are shown in Table 1. Also G_1 was soluble in polar solvents such as: methanol, ethanol, DMSO, DMF and in hot THF and acetone. However, G_1 was not soluble in some of organic solvents such as chloroform, toluene, and dichloromethane but it was swelled in chloroform and dichloromethane (see Table 2).

The compound G_2 was prepared by two routes as shown in Scheme 2. In the first route G_1 was first chlorinated under argon and very dry conditions using thionylchloride, then reacted with citric acid and finally G_2 was obtained.

The absence of absorbance band in FT–IR spectrum (Table 3) of COOH of the citric acid confirmed that the chlorinated reaction was completed. In the second route DCC was used in the preparation of G_2. ^{1}H NMR, FT–IR spectrum and other physical properties of resulted G_2 from both using DCC and thionylchloride were similar. Fig. 1(b) display ^{1}H NMR of G_2, the chemical shifts at 2.9–2.6 ppm (CH_2) of protons of citric acid as a quartet (AB system), protons of PEG at 3.9–3.6 ppm (–OCH_2CH_2O–) and 4.1–4.2 ppm (–$COCH_2O$–) can be recognized. In ^{1}H NMR spectroscopy the comparison of the proton numbers of CH_2 of G_2 shows that the number of protons of citric acid versus number of protons of PEG is grown related to the G_1, which indicates the formation of dendrimer (G_2). Also integral ratio of aliphatic protons of PEG to citric acid is 1.52 (in comparison to 1.6 as a theoretical calculation) shows that the reaction was completed and the growth of dendrimer is confirmed (G_2). When water was added to the G_2 an opaque solution was observed which is related to the aggregation phenomena of G_2. With increasing temperature of opaque solution, it changes to a clear solution and G_2 is dissolved. On cooling, the solution again became opaque. For the determination of transition temperature (gel to solution) the viscosity of G_2 in water solution was measured during gelation. A 4.0 wt.% water solution of G_2 was prepared at 80 °C, transferred to a viscometer at 25 °C, and viscosity was measured as the solution gelated. At the onset of gelation (50–55 °C) the viscosity increased as the solution gelated (Table 1) and we could resulted that the transition temperature of G_2 is 50–55 °C. As mentioned above G_2 was not soluble but it was swelled in chloroform, toluene, and dichloromethane, also it was soluble in methanol, ethanol, DMSO, DMF and in hot acetone solution. The solubility of G_1 was more than G_2 in the above mentioned solvents (see Table 2).

We attempted to synthesize the third generation (G_3). For the chlorination of G_2 the reaction of G_2 with thionylchloride gradually gave a color solution and finally changed to a solid black compound after three days the reaction failed to give the activated compound. Thus, for the preparation of G_3 the reaction of G_2 with citric acid was carried out using DCC in DMF as shown in Scheme 3 and the product was isolated. The Fig. 1(c) shows ^{1}H NMR spectrum of G_3, chemical shifts of protons of citric acid at 2.9–2.6 ppm (CH_2) as a quartet (AB system), protons of PEG at 3.9–3.6 ppm (–OCH_2CH_2O–) and 4.1–4.2 ppm (–$COCH_2O$–) can be recognized also chemical shifts at 2.5 ppm is related to solvent (DMSO). The number of protons of G_3 in the same chemical

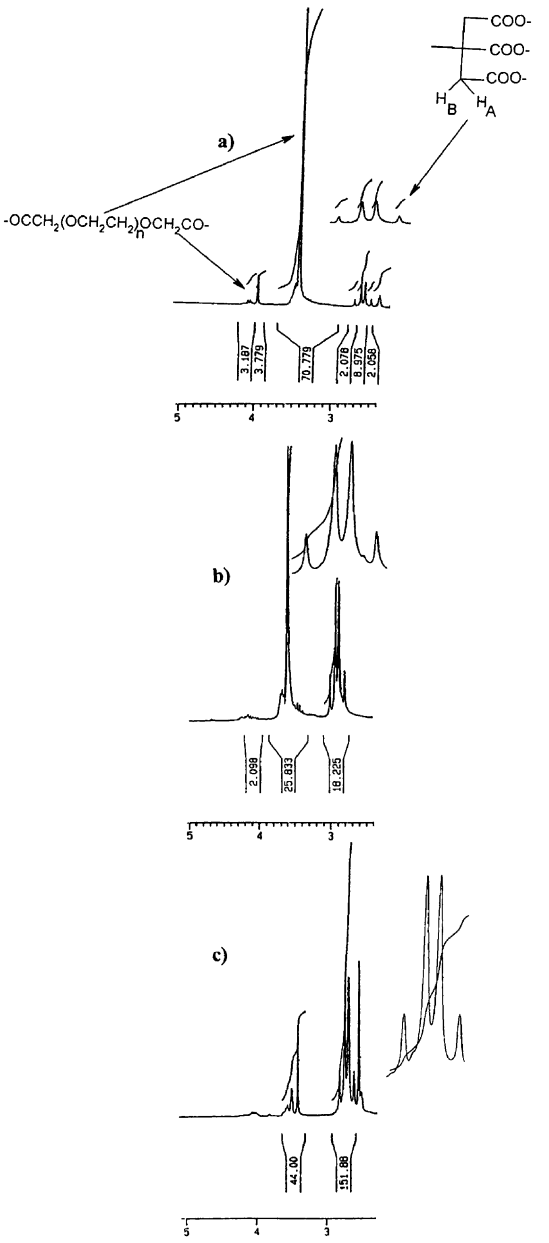


Fig. 1. ^{1}HNMR spectra of (a) G_1 in DMSO-d_6 solvent, (b) G_2 in acetone deuterium solvent and (c) G_3 in DMSO-d_6 in the presence of acetone.

shifts displays the growth of citric acid part in comparison with the protons of poly(ethyleneglycol) as a core and also in G_2. Integral ratio of aliphatic protons of PEG to citric acid is 0.29 (in comparison to 0.5 as a theoretical calculation) which indicates the growth of dendrimer somewhat more than third generation and less than fourth generation thereabout $G_{3.2}$. Also G_3 was soluble in polar solvents such as: methanol, ethanol,

Table 1
Opaque temperature for aqueous solutions of G_1, G_2 and bis-globular/drug gels of G_1 and G_2 in pH 3

Sample	Concentration, wt.%	Temperature, °C
G_1	5	40–45
G_2	5	50–55
Bis-globular/pyridine	5	40–45
Bis-globular/5-ASA	5	55–60
Bis-globular/5,7-dibromo-8-hydroxy	5	62–67

DMSO, DMF and in hot THF. However, G_1 was not soluble in some of organic solvents such as toluene but it was swelled in chloroform, dichloromethane and and hot acetone (see Table 2).

The drug/bis-globular compounds were prepared with addition of drug to bis-globular compounds as mentioned in experimental section. The presence of expected aromatic (C=C and C–H) absorbance band and peaks in the IR (Table 3) and in the aromatic region of ^{1}H NMR of bis-globular/pyridine, bis-globular/5-ASA and 5,7-dibromo-8-hydoxy quinoline complexes display the existence of guest molecules pyridine, 5-ASA and 5,7-dibromo-8-hydroxy quinoline. The mol% drug in drug/bis-globular can be calculated (for example the integrals of ^{1}H NMR in Fig. 3) in the complex.

Calculation of mol% pyridine for G_2/pyridine complex:

The ratio integral of drug protons to integral of CH_2 protons of citric acid = The ratio of the number of drug protons to the number of CH_2 protons of citric acid.

X = mol% of drug and Y = mol% of citric acid

$2.52/4.3 = 5X/32Y$

$X = 0.26Y$ and $X + Y = 1$

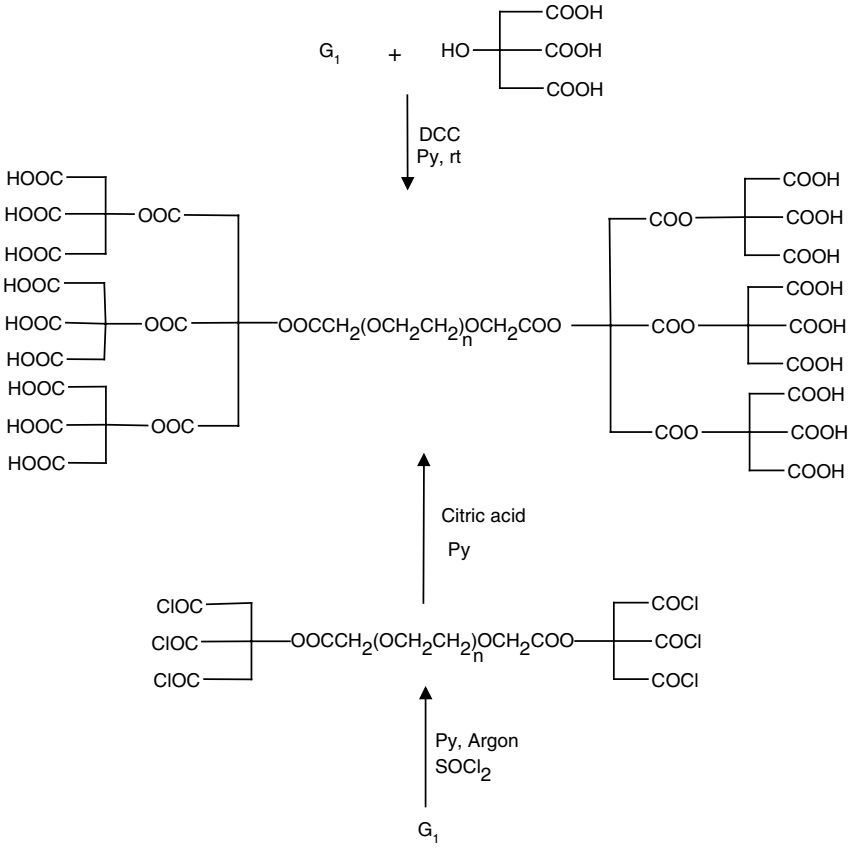
$X = 0.2 \times 100$

$X = 20\%$

Drug/bis-globular compounds of 5,7-dibromo-8-hydroxy quinoline could be dissolved up to several weight percents (5%) in hot solution of ethanol/water (1:4, v/v) or DMF/water (1:4, v/v). The other complexes of pyridine and 5-ASA are easily soluble in hot water solution (10%). On cooling, all of the solutions became opaque indicating the formation of stiff gels as described in the experimental section. For more assurance from the viscosimetry result and determination of transition temperature the optical microscopy was also carried out on the G_1 complexes. The optical microscopy of air-dried prepared semi-solid films and the solution samples of the drugs/bis-globular clearly revealed the formation of gels. Also we concluded the transition temperature from the optical microscopy observations.

Table 2
The solubility behavior of G_1, G_2 in common organic solvents: soluble (*) and insoluble (–)

Solvents	Samples								
	G_1			G_2			G_3		
	Soluble	Insoluble	Swell	Soluble	Insoluble	Swell	Soluble	Insoluble	Swell
Dichloromethane	–	–	*	–	–	*	–	–	*
Chloroform	–	–	*	–	–	*	–	–	*
Toluene	–	*	–	–	–	*	–	*	–
Methanol	*	–	–	*	–	–	*	–	–
Ethanol	*	–	–	*	–	–	*	–	–
DMSO	*	–	–	*	–	–	*	–	–
DMF	*	–	–	*	–	–	*	–	–
THF (hot)	*	–	–	*	–	–	*	–	–
Acetone (hot)	*	–	–	*	–	–	–	–	*

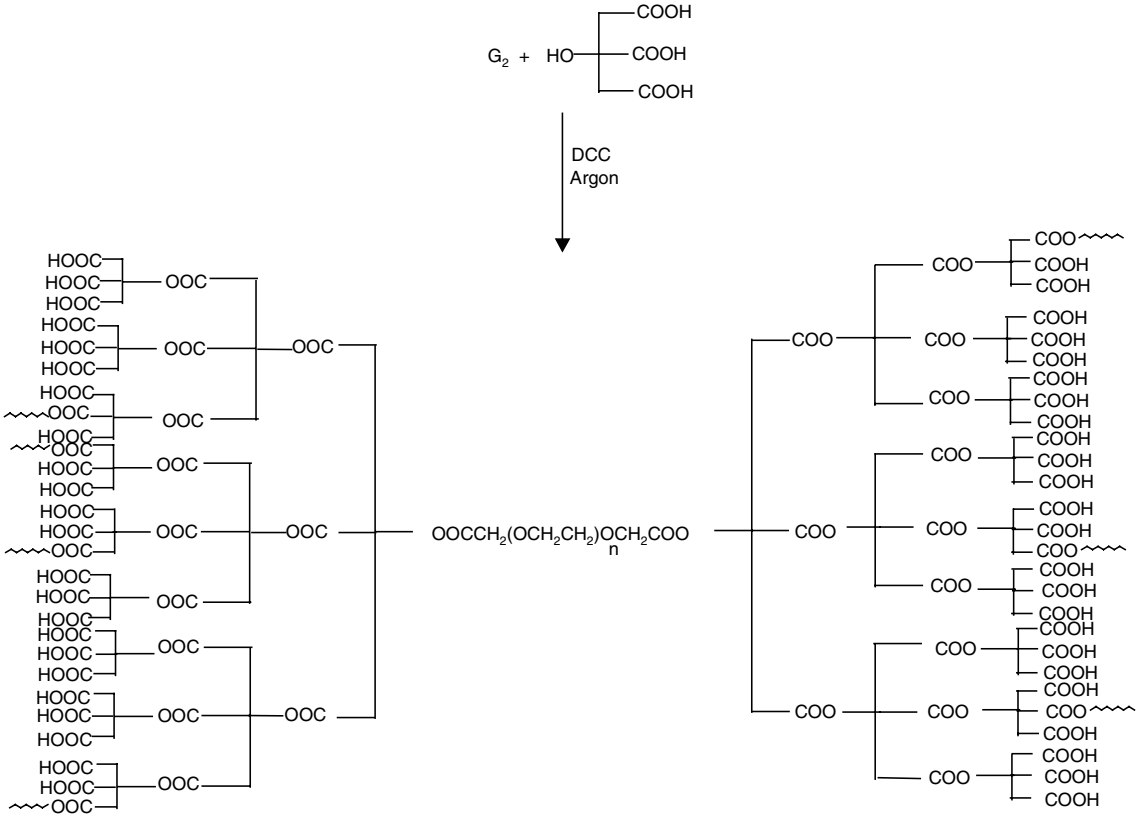


Scheme 2. Synthesis of G_2.

The optical microscopy picture of drugs/bis-globular semi-solid film (air-dried gel) and solution sample (5% wt.) is shown in Fig. 2, the optical microscopy picture (a) of solution sample of the bis-globular/drug (5,7-dibromo-8-hydroxy quinoline) below 62 °C clearly revealed aggregates with a length in the order of 5–40 μm. Picture (Fig. 2(b)) corresponds to the bis-globular/drug (5,7-dibromo-8-hydroxy quinoline) in solution above 67 °C and in this case the aggregations were not observed. Therefore, the transition temperature of bis-globular/

Table 3
FT–IR spectral characteristics of samples (cm^{-1})

Functional groups	COOH	C=C (aromatic)	C=O	C–O
G_1	3501–2650	–	1730–1748	1117, 1202
Chlorinated G_1	–	–	1775–1790	1126–1226
G_2	3501–2637	–	1728–1750	1126, 1209
G_3	3501–2629	–	1725–1745	1119, 1217
Bis-globular/pyridine	3520–2670	1620	1730–1750	1117, 1202
Bis-globular/5-ASA	3520–2650	1620	1732–1749	1120, 1210
Bis-globular/5,7-dibromo-8-hydroxy	3520–2665	1625	1732–1750	1120–1215



Scheme 3. Synthesis of G_3.

(5,7-dibromo-8-hydroxy quinoline) is 62–67 °C. Optical microscopy picture of solution (below 55 °C), and air-dried film sample (Fig. 2(c) and (d)) of the bis-globular/5-ASA displays the presence of aggregates with diameters of 5–20 μm. Optical microscopy picture of solution (above 60 °C) of the bis-globular/5-ASA (Fig. 2(e)) display that above this temperature aggregations were not exist. Therefore, the transition temperature of bis-globular/5-ASA is 55–60 °C.

There are some interesting reports in the ABA dumbbell type copolymers having PEO as the central blocks with different dendritic end groups. The nature of aggregation of this type compounds was investigated by various methods. The characteristics of amphiphiles some of the ABA triblock dendritic in aqueous conditions could be dispersed as the miceller aggregates [30] or as the electrostatic interactions depends on the nature of the end groups in dendritic compound [30]. In this work the nature of aggregation and interactions between host and guest molecules have not clearly understood yet and the type of the interactions seems to be more complex in comparison to the above works. The further

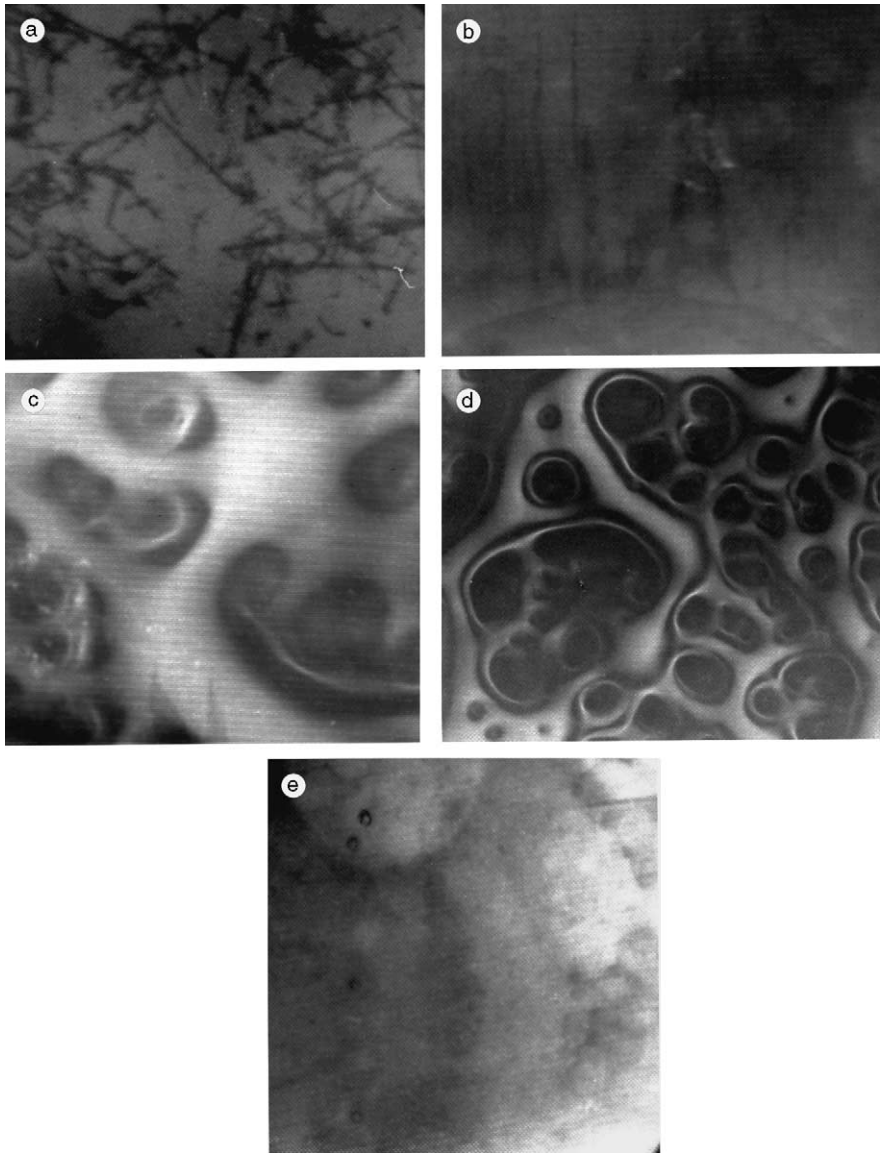


Fig. 2. Optical microscopy pictures with ×500 magnification of (a) solution (5% wt.) of G_1/5,7-dibromo-8-hydroxy quinoline complex (below 67 °C); (b) solution (5% wt.) of G_1/5,7-dibromo-8-hydroxy quinoline complex (above 67 °C); (c) solution (5% wt.) of G_1/5-ASA complex (below 60 °C); (d) air-dried film of G_1/5-ASA complex; (e) solution (5% wt.) of G_1/5-ASA complex (above 60 °C).

investigations using different methods is going on in our laboratory to determine the exact nature of the interactions of host/guest binding. However as shown in the ^{1}H NMR of compound G_2/pyridine in Fig. 3 there is three series of proton absorption in different chemical shifts ($a_1b_1c_1$, $a_2b_2c_2$ and $a_3b_3c_3$) related to pyridine molecule in the complex compound. The three different series chemical shifts indicate the existence of probably different type of interactions with various natures between G_2 (host) and pyridine (guest) molecules.

4. Conclusion

The preparation of bis-globular compounds is possible using the PEG and citric acid, which forms thermoreversible hydrogels. In addition, it was indicated that the resulted compounds are soluble in aqueous solutions and are able to bind and solubilize small polar molecules. When the guest molecules are drug molecules, the resulting complexes could be considered as potentially drug delivery systems. The host–guest properties of the

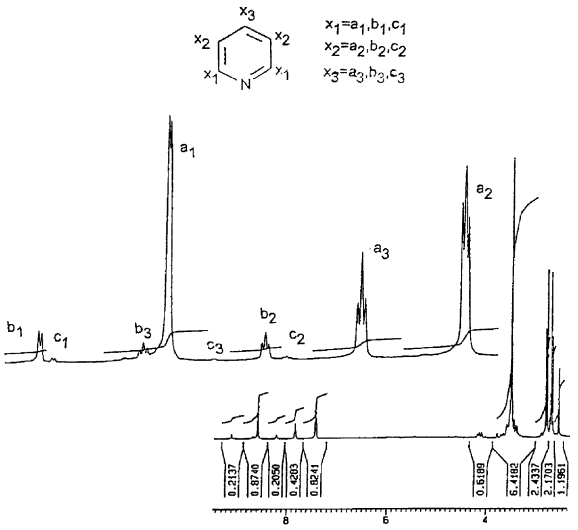


Fig. 3. ^{1}H NMR spectra of G_2/pyridine complex in DMSO-d_6.

synthesized bis-globular compounds as the host molecules and some drug molecules as the guest molecules were investigated using different methods. It seems that several kind of interactions exist between host and guest molecules in which this phenomena as an advantage could be applied for the various type of guest molecules.

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