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The synthesis of novel Linear-globular dendritic copolymer (ABA) using (-) L Ascorbic acid (vitamin C)

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ABSTRACT

Ascorbic acid- polyethylene glycol- ascorbic acid (AA-PEG-AA) triblock dendrimer as biocompatible compound containing G_1, G_2 and G_3 were applied as a drug- delivery system. The syntheses of novel liner- dendritic copolymers were achieved via tow procedures. In the first procedure synthesis of the copolymers carried out through an esteri fication reaction using thionyl chloride and pyridine. In the second procedure copolymers was prepared using dicyclohexylcarbodimide (DCC) and pyridine. The ascorbic acid as the monomer unit was used for the preparation of ester-globular fragments. Diacid poly (ethylene glycol) was chlorinated and diacyl halide poly (ethylene glycol) prepared and used as the core. The structure definition and analysis of the new resulted triblock copolymers and their complexes were carried out using NMR, optical microscopy, FT- IR methods.

KEYWORDS

Ascorbic acid;
Linear-dendriti;
Poly (ethylene glycol);
Dicyclohexylcarbodiimide.

INTRODUCTION

Dendrites are a new class of polymeric belongings[1]. dendrimer chemistry is one of the most attractive and hastily growing areas of new chemistry[2].

Since the dendrimers in troduction in the mid-1980 s, this novel class of polymeric materials attracted considers able attention, because of their unique structure and properties[3].

There are attempts to use dendrimers in the targeted delivery of drugs and other beneficial agents[4]. Today, polymeric structures with very low polydisperity, eg dendrimers, are being preferred as carriers of antitumor drugs[5]. Dendrimers can be used as potential drug-delivery agents in at least two ways. Firstly, the drug molecules can be physically entrapped inside the dendritic structure; secondly, the drug molecules can be covalently attached on to surface or other functionalities to afford dendrimer-drug conjugates[6]. Duncan and co-workers have prepared a PAMAM dendrimer-platinate conjugate and examined its antitumor activity[7]. Prepared the poly (amide–amine) dendrimers with a cyclic core, and attached 5–fluorouracil to the G_4 and G_5 dendrimers to form conjugates[8]. Such complexes may be considered as potential drug delivery systems[9]. An area that has concerned great notice is the contact be-

tween drugs and dendrimers[10]. Several types of interaction have been explored, which can be broadly subdivided into the trap of drug molecules within the dendritic design (involving electrostatic, hydrophobic and hydrogen bond interactions) and the interaction between a drug and the surface of the dendrimers (electrostatic and covalent interactions)[11]. The synthesis of some dendrimers form citric acid, 5–amino salicylic acid and poly (ethylene glycol) (G_1, G_2 and G_3) was reported.

Prepared of some drug/dendrimer complexes containing G_1, G_2 and G_3 of dendritic citric acid-poly (ethylene glycol) - Dendritic citric acid (CPEGC) as the new drug- delivery agents and some guest molecules such as 5-ASA, pyridine, mefenamic acid, and diclofenac[11,12].

EXPERIMENTAL

Materials

Poly (ethylene glycol) 600 diacid (acid number 175, 96-98% from fluka) was dried over Na_2SO_4. Ascorbic acid and pyridine (purified with refluxing over NaOH for 2 hours and subsequent distillation) were supplied by Merck. Thionyl chloride (Merck) was purified by refluxing a mixture of lo wt %. DCC (Merck).

FTIR spectra were obtained by a shimadzu model FT-NMR (400 MHz) Brucker in $COCl_3$. And UV-Vis 2100 shimadzu spectrophotometer was applied.

Diacyl halid poly (ethylene glycol) (PEG-COCl), the diacyl halide poly (ethylene glycol) was prepared by literature metuod[11]. In this procedure, dry poly (ethylene glycol) 600 diacid (PEG–A) was chlorinated with refluxing in thionyl chloride and ClOC-PEG-COCl obtained as the light brown oil, yield 100%.

Preparation of G1 using thionyl chloride

A solution of ascorbic acid (0.637 g, $36.1 \times 10^{-3} \times 2$ mol) in 20 mL dry (DMSO) was placed in a round–bottom flask equipped with a reflux condenser, dropping funnel, nitrogen Intel 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 DMSO 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 nitrogen) then was cooled and filtered off and was precipitated in diethyl ether. Then the product was removed from dialysis bag and dried under vacuum at 50 °C as the reddish oil, brown 70 %.

Chlorination of G_1: A mixture of compound G_1 (0.5 g, 5.27×10^{-4} mol) and dry pyridine (0.3 mol, 3.72×10^{-3} mol) was placed in a round-bottom flask equipped with a reflux condenser, dropping funnel, nitrogen in let and magnetic stirrer.

A much purified thionyl chloride 20 mL was added to the mixture at 0 °C for 30 min. the mixture was stirred to 0 °C for 1 h then refluxed for additional 16 h. the mixture was cooled and filtered off and the excess of thionyl chloride 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 thronyl chloride and finally the larget compound was obtained as the oil brown yield 80 %.

Preparation of G_2 using dicyclohexyl carbodiimide (DCC). A solution of G_1 (2 g, 2.1×10^{-3} mol) in 15 mL dry DMSO was added to a round-bottom flask equipped with reflux condenser. Nitrogen 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 DMSO was added to mixture at 0 °C by dropping funnel. The mixture was stirred for 20 min. Then a solution of ascorbic acid (0.483 g, 2.74×10^{-3} mol) in 10 mL DMSO was added drop wise to this solution. The mixture was stirred at 0 °C for 1 h then at room temperature for 24 h under nitrogen. The product was precipitated in diethyl ether. The product was removed from dialysis bag and dried under vacuum at 50 °C as amorphous compound, yield (80%).

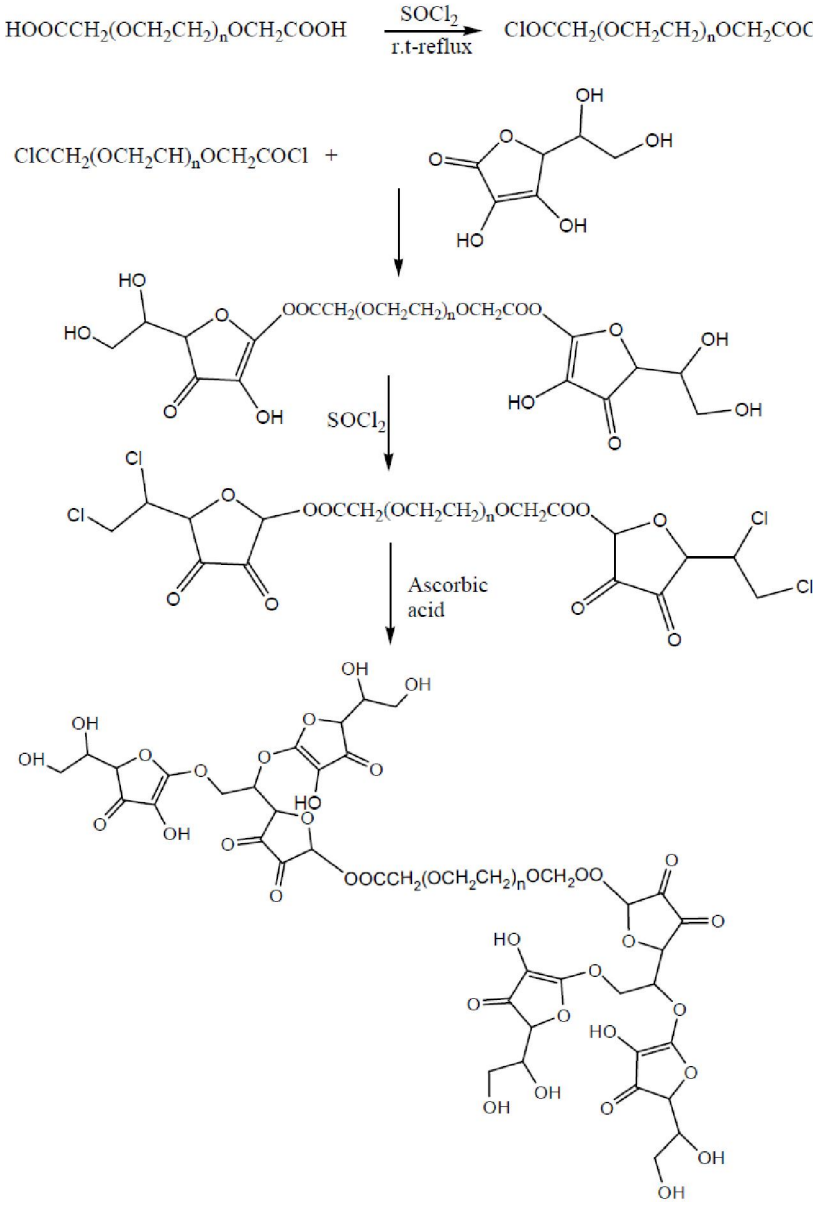
Preparation of G_3 using DCC: A solution of G_2 (2 g, 1×10^{-3} mol) in 15 mL dry DMSO was added to

a round-bottom flask equipped with reflux condenser, nitrogen 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 DMSO was added to mixture at 0 °C by dropping funnel. The mixture was stirred for 20 min. Then a solution of ascorbic acid (0.288 g, 1.5×10^{-3} mol) in 10 mL of DMSO was added drop wise to this solution. The mixture was stirred at 0 °C for 1.5 h then for additional 72 h under nitrogen 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 diethyl ether. The mixture was conducted in to cellophane membrane dialysis bag.

RESULTS AND DISCUSSION

Compound G_1 was synthesized through the reaction of ClOC-PEG-COCl with anhydrous ascorbic acid and also ClOC-PEG-COCl was prepared in the chlorination reaction of diacid poly (ethylene glycol) using thionylchloride in yield 100 %, this is shown in scheme 1. Compound G_2 was prepared



Scheme 1 : The preparation routes of G_1 and G_2

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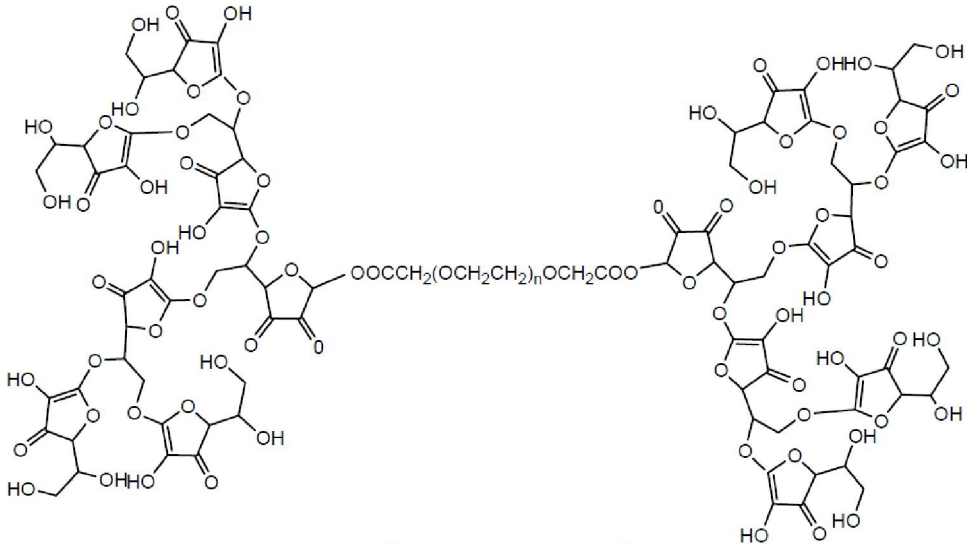

Scheme 2 : The preparation routes of G_3

TABLE 1 : FT-IR spectral characteristics of samples (cm^{-1})

Functional groups	O-H	C=C (aromatic)	C=O	C-O
G_1	3460	1660	1660	1100
Chlorinated G_1	--	1657 (weak)	1737	1464
G_2	3456	1666	1666	1095
G_3	3475	1670	1670	1095

TABLE 2 : ^{1}HNMR data of G_1, G_2 and G_3

Compound	Solvent	^{1}HNMR / σ ppm^{-1}				
		OCH_2	$CH_2C=O$	CHO	CH(aromatic)	CHOH
G_1	$CDCl_3$	3.6	2.7	4.8	7.9	2.8-2.9(doublet)
G_2	$CDCl_3$	3.6	2.2	5.1	8	2.8-2.9(doublet)
G_3	$CDCl_3$	3.6	2.5	4.8	7.9	2.7-2.8(doublet)

using G_1 and DCC, and then reacted with ascorbic acid.

For the preparation of G_3 the reaction of resulted compound G_2 with ascorbic acid was carried out using DCC in DMSO and the product was isolated, this is shown in scheme 2.

The absorbed bonds in IR spectra (C=C) (C=O) can be the chemical shifted 1660 cm^{-1} also conjugate was completed, The results showed in TABLE 1.

The absence of absorbance band in FT-IR spectrum of O-H of the ascorbic acid confirmed that the chlorinated reaction, the results showed in TABLE 1.

The ^{1}HNMR of G_1 which shows a doublet at 2.8-2.9 ppm, 4.8 and 7.9 ppm as an AB system for the CH_2 protons of ascorbic acid, This is shown in TABLE 2.

The protons of PEG at 3.6 ppm (-OCH_2CH_2)-O and 2.7 ppm (-$COCH_2$O-) can also be recognized the chemical shifted 7.3 ppm is related to the $CDCl_3$ as the solvent. (The integral ratio of aliphatic protons of PEG to the ascorbic acid part of the mdecule is 8 (in comparison to 8 as a theoretical calculation). The absence of absorbance band in FT-HNMR spectrum of COOH the ascorbic confirmed that the G_1 reaction[13].

Display ^{1}HNMR of G_2, the chemical shifts at 2.8-2.9 ppm (CH_2) of protons of ascorbic acid as a doublet, protons of PEG 5.1 ppm (-$COCH_2$O-) can be recognized.

In ^{1}HNMR spectroscopy the comparison of the proton numbers of CH_2 of G_2 shows that the number of protons of ascorbic acid versus number of pro-

tons of PEG is grown related to the G_1, Which indieates the formation of dendrimer (G_2). Also integral ratio of aliphatic protons of PEG to ascorbic 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). ^{1}HNMR spectrum of G_3, chemical shifts of protons of ascorbic acid at 2.7-2.8 ppm (CH_2) as a doublet and 7.9ppm (AB system).

Protons of PEG at 3.6 ppm (-OCH_2CH_2)-O and 2.5ppm (-$COCH_2$O-).the number of protons of G_3 in the same chemical shifts displays the growth of ascorbic acid part in comparison with the protons of poly (ethylene glycol) as a core and also in G_2.

Integral ratio of aliphatic protons of PEG to ascorbic acid is 0.29 (in comparison to 0.5 as a theoretical calculation).

Preparation of samples for UV experiments

The maximum absorption of the dendrimer was determined by UV spectrophotometer using a lem quartz cell.

A solution of dendrimer was prepared and left at room temperature overnight; then it was filtered by micro filters.

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