Synthesis and Characterization of Bile Acid-Based Poly β Amino Esters for Paclitaxel Delivery

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ABSTRACT: New biodegradable poly β amino esters were synthesized by the polymerization of Deoxycholic acid (DOCA) in all the structural planes by 1, 4 addition of Trimethylene dipiperidine (TMDP) to diacrylates of Deoxycholyl glycol, Methyl deoxycholate and Trimethylolpropane deoxycholate esters. ^{1}H-NMR, ^{13}C-NMR and IR studies confirmed presence of amine and Deoxycholyl units in polymers. XRD and TGA studies indicated that all the polymers were amorphous and thermostable up to 300°C. DSC studies revealed glass transition temperature (T_g) in the range 70–80°C. All the polymers degraded very slowly in the buffers of pH 1.1, 7.4 and 10 because of the hydrophobic nature of Deoxycholate units. These polymers also exhibited pH sensitivity due to the incorporation of amines along with Deoxycholate units in the backbone. P-Nitroaniline (PNA) release followed anomalous release kinetics. Paclitaxel (PTX) loaded nanospheres prepared from these polymers were spherical and uniform in the size range 75–250 nm and 0.4–1μ depending upon the method of preparation. PTX loading was in the range 60–90%, while release (up to 20–60%) was sustained over a period of 100 h. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 122: 220–232, 2011

Key words: bile acid; poly β amino esters; Paclitaxel; nanoparticles; biodegradable

INTRODUCTION

Designing materials for biomedical applications and drug delivery has always been a challenge in view of the stringent requirements of mechanical strength, biocompatibility, and biodegradability. Currently used synthetic biodegradable polymers are mostly polyesters viz. polylactic acid (PLA), polylactic glycolic acid (PLGA), and polycaprolactone (PCL). Among these, PCL offers enhanced biocompatibility, higher hydrophobicity, and neutral degradation end products which do not alter the pH of the degradation medium like PLA and PLGA.[1–5]

Bile acids are biological compounds present in the gastrointestinal tract. Their amphiphilicity and rigid structure makes them suitable building blocks for the synthesis of degradable polymeric materials. These materials would exhibit tunable mechanical and interfacial properties as well as better biocompatibility.[6–9] In the past, bile acids have been polymerized as side chain pendants,[10–12] in main chain,[13,14] and as chain end groups.[15] However, reports on main-chain bile acid based polyesters, polyamides, and polyurethanes are relatively few.[13] Lipase and coupling agents like PTSA and Dicarboimidazole (DCI) with DMAP yielded highly crystalline and rigid polymers of DOCA and Lithocholic acid which exhibited poor solubility in organic solvents. Degradation of polyanhydrides based on bile acid and Sebacic acid could be tuned by varying comonomer ratios. However, their utility was limited by low glass transition temperature (T_g) 13°C.[14] Cholic acid functionalized branched polycaprolactones had melting points above room temperature, were soluble in common organic solvents, and exhibited melt viscosities suitable for processing in tissue engineering applications.[16]

Synthesis of polyesters with bile acids in the main chain via entropy driven ring-opening polymerization using Grubbs catalyst yielded high molecular weight bile acid polymers obviating the need for coupling agents.[13] However, this approach suffers from quite a few limitations: (1) It involves preparation and use of catalyst; (2) Bile acids with functionality on steroidal nucleus would need protections before lactone preparation and its polymerization. (3) Polymers exhibited too low T_g (2–15°C) to be useful in drug delivery applications. More recently, polymerization of bile acids using click chemistry yielded high molecular weight main chain bile acid polymers.[17] Degradability of most of these polymers was compromised due to lack of readily hydrolysable linkage which limited their applications in drug delivery.

Synthesis of linear poly(amino esters) and poly (amido amines) containing tertiary amines in their backbone were reported by Ferruti et al.[18,19] and

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more recently by Lynn and Langer.[20] These polymers were synthesized by the addition of bifunctional amines to bisacrylamides and diacrylates. Analogous poly (ester sulfides) and poly (amino esters) synthesized from diacrylates have been reported to degrade due to the hydrolytic instability of the ester linkages. The absence of possibility of a retro-Michael addition in these systems eliminates the possibility of generation of carcinogenic diacrylate during degradation.[21]

Poly (β amino ester) utility has been limited mostly due to processability ascribed to low T_g values. Polymers based on bile acid are expected to exhibit high T_g values because of their rigid steroidal structure. To the best of our knowledge, steroidal nucleus has not been reported as building block in poly β amino ester synthesis. We synthesized different steroidal diacrylates using hydroxyls on Deoxycholate esters at carbon 3, 12, 26, 29, and 30. The bile acid-based poly β amino esters were prepared by Michael addition of Trimethylene dipiperidine (TMDP) to Deoxycholate diacrylates using $AlCl_3$ as catalyst. The addition could lead to the incorporation of Deoxycholate moiety in polymer backbone as (1) head to tail, (2) head to side, and (3) pendent through tail. The β amino ester linkage would impart pH sensitivity to bile acid polymer and also incorporate hydrolysable linkages between DOCA units which would accelerate the degradation. The steroidal diacrylates and poly β amino esters have been characterized by ^{1}H-NMR, GPC, IR, TGA, DSC, and XRD. Degradability of these polymers has been investigated at three different pH viz. 1.1, 7.4, and 10. Release of PNA as a model compound has been monitored from these polymer matrices in phosphate buffer (pH 7.4). PTX loading and release from nanoparticles indicates the potential for drug delivery. Low molecular weight and cationic charge also suggest utility for gene delivery applications.

EXPERIMENTAL

Materials

Deoxycholic acid (DOCA), Acrylic acid, Trimethylolpropane (TMP), and Trimethylene dipiperidine (TMDP) were purchased from Sigma–aldrich and used as received. Triethylamine (TEA), Methanol, Dichloromethane (DCM), Aluminum trichloride ($AlCl_3$), Chloroform, Ethylene glycol (EG), Benzoyl chloride, concentrated Hydrochloric acid (HCl), and P-Nitroaniline (PNA) were purchased from Merck India. Acryloyl chloride was freshly prepared from Acrylic acid and Benzoyl chloride. Paclitaxel (PTX) was generous gift from Cadilla pharma, India.

Synthesis of bile acid-based poly β amino ester

Different approaches have been explored in this work to polymerize Deoxycholate diacrylates using 1, 4 Michael addition of an amine such as TMDP. In the polymeric bile acids, Deoxycholate units have been incorporated in the backbone as head to tail conjugated β amino ester, i.e., C_3 and C_{26} polyaddition, head to side conjugated β amino ester, i.e., C_3 and C_{12} polyaddition, and as a pendent group through tail to β amino ester backbone, i.e., C_{29} and C_{30} polyaddition.

C_3 and C_{26} polyaddition [poly (Deoxycholyl glycol TMDP β amino ester)]

Deoxycholyl glycol ester (DG)

DOCA (10 g, 25.5 m*M*) was dispersed in 100 mL EG. The mixture was stirred for 10 min and HCl (2 mL) was added. Stirring was continued for another 10 min and the mixture was heated at 55–60°C for 8 h. This solution was slowly added to 2 L of cold water and the resultant precipitate was filtered, washed, and dried. This step was repeated once again to completely remove traces of EG. Finally, the product was dried under vacuum at 50°C for 2 days and stored in desiccator. (Melting point 140°C, Yield 11.3 g) (Scheme 1).

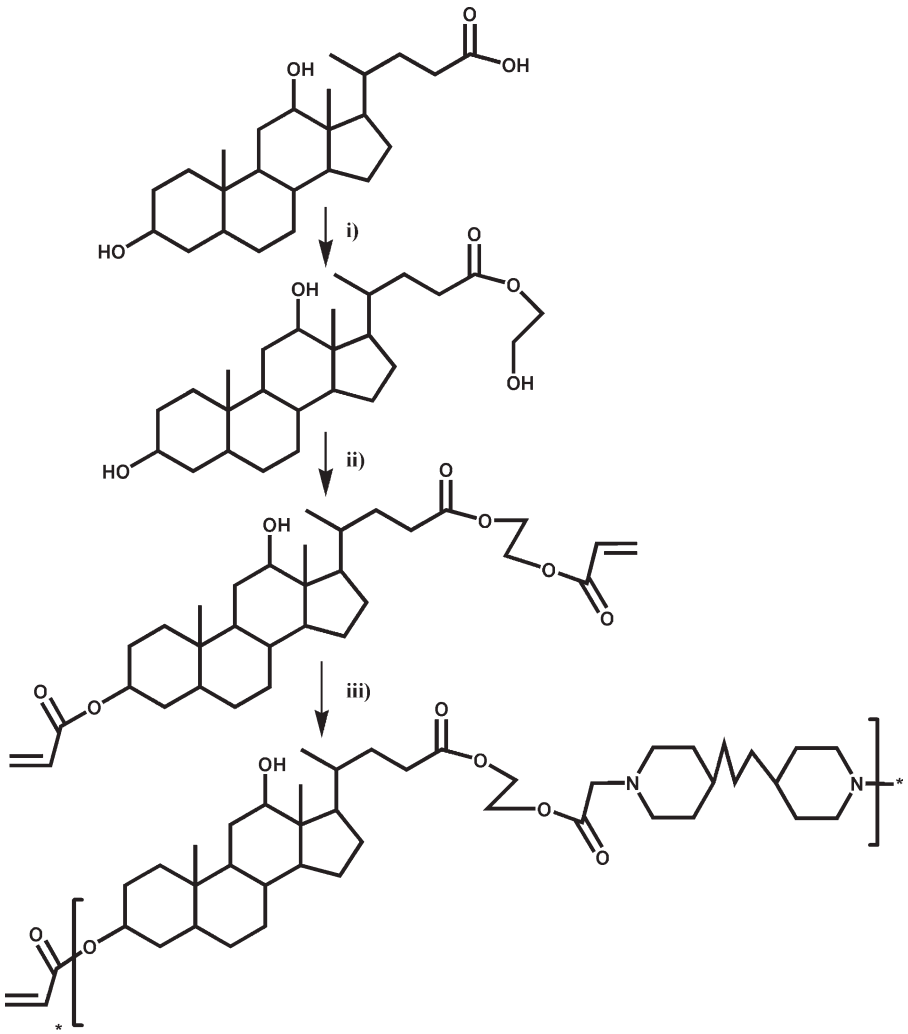
^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.68 (s, 3H), 0.91 (s, 3H), 1 (d, 3H), 0.95–2.16 (m, steroidal CH, CH_2), 3.26 (m, 3H), 3.61 (m, 1H), 3.82 (d, 2H), 3.98 (t, 1H), 4.21 (d, 2H).

Deoxycholyl glycol diacrylate (DGDA)

DG (11 g, 25.2 m*M*) was dissolved in 200 mL of dry THF. TEA (4.2 mL, 30 m*M*) was added and the solution was stirred for 30 min under Nitrogen atmosphere at 2–8°C. Acryloyl chloride (2.9 g, 29.2 m*M*) in 30 mL of THF was added drop wise for 1 h and stirred overnight. The reaction mixture was filtered to remove TEA hydrochloride salt. The filtrate was concentrated and purified by silica gel column chromatography using ethyl acetate : petroleum ether as eluent. (R_f 0.28 in 25 : 75 ethyl acetate: pet ether mixture) (Yield 6.9 g).

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.68 (s, 3H), 0.93 (s, 3H), 0.99 (d, 3H), 0.95–2.16 (m, steroidal CH, CH_2), 2.46 (m, 2H), 4.00 (m, 1H), 4.40 (m, 4H), 4.58 (br d, 2H), 6.13 (br d, 2H), 6.41(br d, 2H).

^{13}C-NMR (200 MHz, $CDCl_3$, 77.00) δ: 12.67 (—**CH_3**, C_{18}), 17.23 (—**CH_3**, C_{19}), 23.05 (—**CH_2**—, C_{15}), 26.87 (—**CH_2**—, C_{16}), 30.71 (—**CH_2**—, C_{22}), 30.98 (—**CH_2**—COO, C_{23}), 33.57 (C—**CH_2**—C, C_1), 34.08 (C—**CH_2**—C C_4), 34.97 (**CH,** C_{20}), 35.89 (**CH,** C_8), 41.77 (**CH,** C_5), 46.41 (**C,** C_{13}), 47.22 (**CH**, C_9), 48.20 (**CH**, C_{17}), 61.87 (—**CH_2**—), 62.26 (—**CH_2**—),73.02 (C—**CH**—O, C_3), 74.35 (C—**CH**—OH, C_{12}), 127.90



Scheme 1 Synthesis of poly (Deoxycholyl glycol TMDP β amino ester). i) Ethane diol, conc. HCl, 8 h, 55–60°C; ii) Acryloyl chloride, TEA, THF, 24 h; iii) TMDP, $AlCl_3$, DCM, 24 h.

(**CH**=), 129.01 (=**CH$_2$**), 131.36 (=**CH$_2$**), 165.74 (**CO**—CH=CH$_2$), 173.92 (CH$_2$—**CO**O—, C_{24}).

Poly (Deoxycholyl glycol TMDP β amino ester) [poly (DGDA-*co*-TMDP); C_3C_{26}]

DGDA (2 g, 3.68 m*M*) was dissolved in 20 mL of dry DCM and a pinch of anhydrous $AlCl_3$ was added under Nitrogen atmosphere. This solution was maintained for 15 min under stirring and cooled to 5–10°C. TMDP (0.772 g, 3.68 m*M*) in 10 mL DCM was added slowly to the activated Deoxycholyl glycol diacrylate solution and stirred for 24 h at room temperature. It was then washed with brine and dried over anhydrous sodium sulfate and concentrated. The polymers obtained were washed with hexane and dried under vacuum for 8 h to yield poly (DGDA-*co*-TMDP) powder. (Yield 2.34 g)

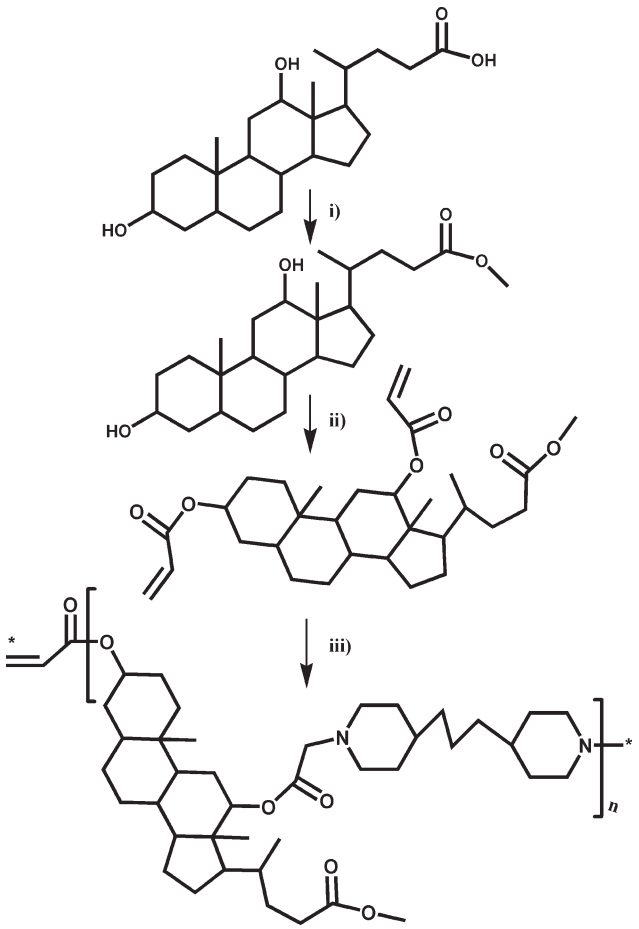
^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.68 (s, 3H), 0.91 (s, 3H), 0.99 (d, 3H), 0.95–2.06 (m, steroidal and TMDP CH, CH2), 2.33 (m, 2H), 2.51 (m, 4H), 2.68 (d, 4H), 2.85 (d, 4H), 4.00 (m, 1H), 4.40 (m, 4H), 4.80 (m, 1H), 5.83 (br d, 0.06H), 6.10 (d, 0.06H), 6.34 (br d, 0.06H).

^{13}C-NMR (200 MHz, $CDCl_3$, 77.00) δ: 12.70 (—**CH$_3$**, C_{18}), 17.24 (—**CH$_3$**, C_{19}), 23.07 (—**CH$_2$**—, C_{15}), 26.88 (—**CH$_2$**—, C_{16}), 30.67 (—**CH$_2$**—, C_{22}), 31.05 (—**CH$_2$**—COO, C_{23}), 32.21 (C—**CH$_2$**—C, C_1), 34.05 (C—**CH$_2$**—C C_4), 34.80 (**CH,** C20), 35.50 (**CH,** C_8), 41.77 (**CH,** C_5), 46.41 (**C,** C_{13}), 47.26 (**CH**, C_9), 48.19 (**CH**, C_{17}), 53.69 (CH$_2$—**CH$_2$**—N, TMDP), 61.92 (—**CH$_2$**—), 72.94 (C—**CH**—O—CO—, C_3), 74.16 (C—**CH**—OH, C_{12}), 172.15 (**CO**—CH=CH$_2$), 173.89(CH$_2$—**CO**O—, C_{24}).

C_3 and C_{12} polyaddition [poly (Methyl deoxycholate TMDP β amino ester)]

Methyl deoxycholate (MD)

DOCA (50 g) was dissolved in 250 mL dry methanol, HCl (5 mL) was added to it and the solution



Scheme 2 Synthesis of poly (Methyl deoxycholate TMDP β amino ester). i) Methanol, conc. HCl, 1 h, reflux; ii) Acryloyl chloride, TEA, THF, 24 h; iii) TMDP, $AlCl_3$, DCM, 24 h.

was refluxed for 1 h. The reaction mixture was stored in refrigerator at 2–8°C to crystallize product. The product was filtered and washed with cold methanol to remove DOCA and hydrochloric acid impurities. Final product was dried under vacuum to ensure complete removal of residual methanol. (Melting point 120°C, Yield 24 g) (Scheme 2).

^{1}H-NMR (200 MHz, DMSO d_6) δ: 0.58 (s, 3H), 0.83 (s, 3H), 0.91 (d, 3H), 1–2.0 (m, steroidal CH, CH_2), 2.26 (m, 2H), 3.56 (s, 3H), 3.78 (s, 1H).

Methyl deoxycholate diacrylate (MDDA)

MD (10 g, 24.5 m*M*) was added to 100 mL of dry DCM. TEA (13.6 mL, 96 m*M*) was added and stirred for 30 min under Nitrogen atmosphere at 2–8°C. Acryloyl chloride solution (8.8 g, 94 m*M*) in 40 mL DCM was added over 1 h and stirred for 24 h at room temperature. This solution was washed with 1*N* Hydrochloric acid and brine solution to remove TEA hydrochloride salt. The solution was concentrated and purified by silica gel column chromatography using ethyl acetate: petroleum ether as eluent. (R_f 0.2 in 10 : 90 ethyl acetate: pet ether mixture) (Yield 3.7 g).

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.75 (s, 3H), 0.81 (d, 3H), 0.92 (s, 3H), 1–2.16 (m, steroidal CH, CH_2), 2.25 (m, 2H), 3.65 (s, 3H), 4.10 (m, 1H), 4.76 (m, 1H), 5.17 (t, 1H), 5.82 (br d, 2H), 6.15 (br d, 2H), 6.41(br d, 2H).

^{13}C-NMR (200 MHz, $CDCl_3$, 77.00) δ: 12.36 (—**CH_3**, C_{18}), 17.34 (—**CH_3**, C_{19}), 23.01 (—**CH_2**—, C_{15}), 25.83 (—**CH_2**—, C_{16}), 30.72 (—**CH_2**—, C_{22}), 30.88 (—**CH_2**—COO, C_{23}), 32.15 (C—**CH_2**—C, C_1), 34.40 (C—**CH_2**—C C_4), 34.64 (**CH,** C_{20}), 35.80 (**CH,** C_8), 41.73 (**CH,** C_5), 45.14 (**C,** C_{13}), 47.63 (**CH**, C_9), 49.58 (**CH**, C_{17}), 51.48 (COO—**CH_3**), 74.32 (C—**CH**—O—CO—, C_3), 75.97 (C—**CH**—O—CO—, C_{12}), 128.40 (**CH**=), 130.10 (**CH**=), 130.54 (=**CH_2**), 133.64 (=**CH_2**), 165.74 (**CO**—CH=CH_2), 174.66 (CH_2—**CO**O—, C_{24})

Poly (Methyl deoxycholate TMDP β amino ester) [poly (MDDA-*co*-TMDP); C_3C_{12}]

MDDA (2 g, 3.9 m*M*) was dissolved in 20 mL of dry DCM and pinch of anhydrous $AlCl_3$ was added as a catalyst under Nitrogen atmosphere. This solution was stirred for 15 min and cooled to 5–10°C. To this solution, TMDP (0.82 g, 3.9 m*M*) in 10 mL DCM was slowly added and stirred for 24 h at room temperature. The solution was then washed with brine, dried over anhydrous sodium sulfate and concentrated. The polymer obtained was washed with hexane and dried under vacuum for 8 h to yield poly (MDDA-*co*-TMDP) powder. (Yield 2.25 g)

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.72 (s, 3H), 0.81 (d, 3H), 0.90 (s, 3H), 1–2.16 (m, steroidal CH, CH_2), 2.26 (m, 2H), 2.52 (d, 2H), 2.67 (m, 4H), 2.91 (t, 3H), 3.65 (s, 3H), 4.70 (m, 1H), 5.17 (d, 1H), 5.85 (br d, 0.3H), 6.25 (br d, 0.3H), 6.40 (br d, 0.3H).

^{13}C-NMR (200 MHz, $CDCl_3$, 77.00) δ: 12.33 (—**CH_3**, C_{18}), 17.43 (—**CH_3**, C_{19}), 23.01 (—**CH_2**—, C_{15}), 25.85 (—**CH_2**—, C_{16}), 30.75 (—**CH_2**—, C_{22}), 31.04 (—**CH_2**—COO, C_{23}), 32.16 (C—**CH_2**—C, C_1), 33.98 (C—**CH_2**—C C_4), 34.64 (**CH,** C_{20}), 35.60 (**CH,** C_8), 41.73 (**CH,** C_5), 45.03 (**C,** C_{13}), 47.53 (**CH**, C_9), 49.55 (**CH**, C_{17}), 51.45 (COO—**CH_3**), 53.80 (CH_2—**CH_2**—N, TMDP), 74.11 (C—**CH**—O—CO—, C_3), 75.76 (C—**CH**—O—CO—, C_{12}), 128.86 (**CH**=), 130.50 (=**CH_2**), 165.55 (**CO**—CH=CH_2), 174.59 (CH_2—**CO**O—, C_{24})

C_{29} and C_{30} polyaddition [poly (Trimethylolpropane deoxycholate TMDP β amino ester)]

Trimethylolpropane deoxycholate (TMPD)

DOCA (15 g, 38.2 m*M*) and TMP (150 g, 1.11 m*M*) were mixed. The mixture was heated at 75°C under Nitrogen atmosphere then HCl (2 mL) was added and stirred till DOCA was dissolved completely. Stirring was continued at 65–70°C for 15 h. This solution

was added slowly in 4 L of cold water, stirred and filtered. The product was washed and dried under vacuum. This step was repeated once again to completely remove traces of TMP and Hydrochloric acid. Finally product was dried in vacuum oven at 50°C for 2 days and then stored in desiccator. (Melting point 147°C, Yield 15.9 g) (Scheme 3).

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.68 (s, 3H), 0.88 (m, 6H), 1 (d, 3H), 1.1–2.16 (m, steroidal CH, CH_2), 2.35 (m, 2H), 3.0 (s, 1H), 3.57 (m, 5H), 3.98 (t, 1H), 4.18 (s, 2H).

Trimethylolpropane deoxycholate diacrylate (TMPDDA)

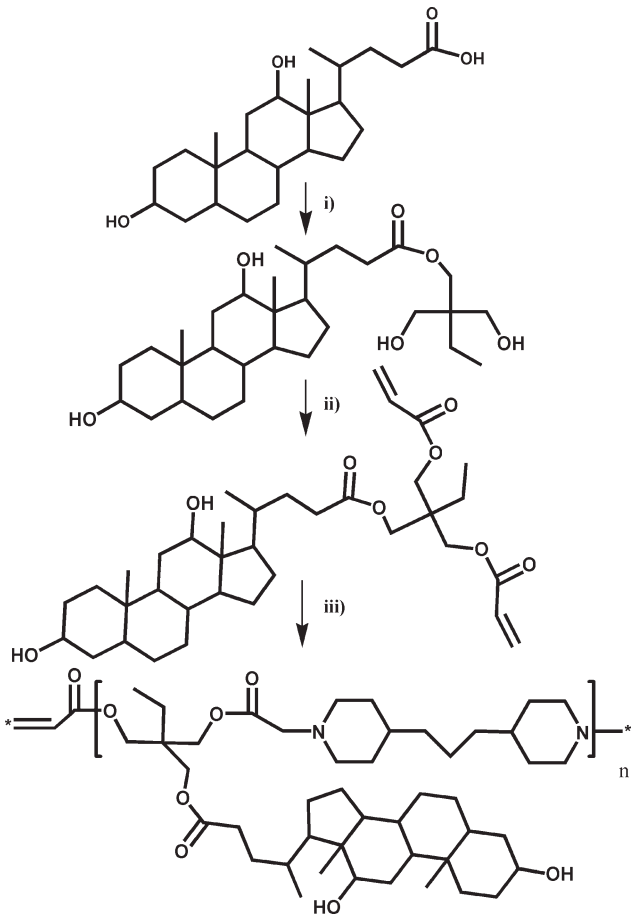
TMPD (15 g, 29.5 m*M*) was dissolved in 300 mL of dry THF. TEA (8.2 mL, 59 m*M*) was added to it and stirred for 30 min under nitrogen atmosphere at 10°C. Acryloyl chloride (5.3 g, 58.8 m*M*) in THF solution was added over 1 h. This reaction mixture was stirred for 24 h at room temperature and then filtered to remove TEA hydrochloride salt. The filtrate was concentrated and purified by silica gel column chromatography using ethyl acetate: petroleum ether mixture as eluent. (R_f 0.13 in 25 : 75 ethyl acetate: pet ether mixture) (Yield 2.4 g)

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.68 (s, 3H), 0.92 (m, 9H), 1.12 (m, 3H), 1.15–2 (m, steroidal CH, CH_2), 2.33 (m, 3H), 2.82 (s, 2H), 3.43 (s, 2H), 3.99 (t, 1H), 4.04 (s, 1H), 4.11 (s, 1H), 4.78 (m, 1H), 5.82 (br d, 2H), 6.14 (br d, 2H), 6.37 (br d, 2H).

^{13}C-NMR (200 MHz, $CDCl_3$, 77.00) δ: 7.24 (—CH_3), 12.67 (—CH_3, C_{18}), 17.20 (—CH_3, C_{19}), 23.13 (—CH_2—, C_{15}), 25.95 (—CH_2—, C_{16}), 30.80 (—CH_2—, C_{22}), 31.06 (—CH_2—COO, C_{23}), 33.59 (C—CH_2—C, C_1), 34.08 (C—CH_2—C C_4), 34.98 (CH, C_{20}), 35.90 (CH, C_8), 41.78 (CH, C_5), 46.41 (C, C13), 48.20 (CH, C_{17}), 62.17 (—CH_2—), 63.71 (—CH_2—), 63.90 (—CH_2—), 73.10 (C—CH—O—CO—, C_3), 74.40 (C—CH—O—CO—, C_{12}), 127.92 (CH=), 129.00 (CH=), 130.26 (=CH_2), 131.46 (=CH_2), 165.81(CO—CH=CH_2), 166.36 (CO—CH=CH_2), 174.56 (CH_2—COO—, C_{24}).

Poly (Trimethylolpropane deoxycholate TMDP β amino ester) [poly (TMPDDA-*co*-TMDP); $C_{29}C_{30}$]

TMPDDA (2.15 g, 3.48 m*M*) was dissolved in 20 mL dry DCM and pinch of anhydrous $AlCl_3$ was added under nitrogen atmosphere. This solution was maintained for 15 min under stirring and chilled to 5–10°C. Slowly TMDP (0.731 g, 3.48 m*M*) in 10 mL DCM was added to the activated Trimethylolpropane deoxycholate solution and stirred for 24 h at room temperature. The solution was washed with brine and dried over anhydrous sodium sulfate and concentrated. The polymer obtained was washed with hexane and dried under vacuum for 8 h to yield poly (TMPDDA-*co*-TMDP) powder. (Yield 2.33 g).



Scheme 3 Synthesis of poly (Trimethylolpropane deoxycholate TMDP β amino ester).i) Trimethylolpropane, conc. HCl, 15 h, 65°C; ii) Acryloyl chloride, TEA, THF, 24 h; iii) TMDP, $AlCl_3$, DCM, 24 h.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.68 (s, 3H), 0.84 (s, 1H), 0.88 (s, 2H), 0.92 (s, 4H), 0.99 (d, 3H), 1.0–2.16 (m, steroidal CH, CH_2), 2.56 (t, 4H), 2.69 (m, 4H), 2.91 (d, 4H), 3.43 (s, 2H), 3.99 (t, 1H), 4.04 (m, 5H), 4.11 (s, 1H), 4.73 (m, 1H), 5.30 (s, 1H), 5.83 (br d, 0.11H), 6.10 (br d, *J* 0.11H), 6.34(br d, 0.11H).

^{13}C-NMR (200 MHz, $CDCl_3$, 77.00) δ: 7.32 (—CH_3), 12.70 (—**CH_3**, C_{18}), 17.23 (—**CH_3**, C_{19}), 23.08 (—**CH_2**—, C_{15}), 25.97 (—**CH_2**—, C_{16}), 30.83 (—**CH_2**—, C_{22}), 31.77 (—**CH_2**—COO, C_{23}), 32.37 (C—**CH_2**—C, C_1), 34.07 (C—**CH_2**—C C_4), 35.01 (**CH,** C_{20}), 35.90 (**CH,** C_8), 42.34 (**CH,** C_5), 46.42 (**C,** C_{13}), 48.22 (**CH**, C_{17}), 53.73 (CH_2—**CH_2**—N, TMDP), 62.38 (—**CH_2**—), 63.77 (—**CH_2**—), 64.32 (—**CH_2**—), 72.99 (C—**CH**—OH, C_3), 74.34 (C—**CH**—OH, C_{12}), 167.69(**CO**—CH=CH_2), 174.37 (CH_2—**CO**O—, C_{24}).

CHARACTERIZATION

^{1}H and ^{13}C-NMR analysis

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX-200 operating at 200.0

MHz for ^{1}H and ^{13}C in $CDCl_3$, which also served as an internal reference (chemical shifts δ H 7.27 and 77).

Size exclusion chromatography (SEC)

Molecular weights of all the polymers (5 mg/mL in Chloroform) were determined by SEC using Waters 410 system at 30°C. The flow rate was 1 mL/min and molecular weights are reported against polystyrene standards.

FTIR spectroscopy

All the polymers were analyzed by FTIR using a Perkin–Elmer, Spectrum One (Transmittance mode). 5–6 mg of sample was thoroughly mixed and triturated with potassium bromide (100 mg) and placed in the sample holder. All the samples were scanned 5 times, at resolution 4 and in the range 4000 to 450 cm^{-1}.

X-ray diffraction (XRD)

The polymer samples were characterized by X-ray diffraction on Philips PW1030 equipment running with CoKα radiation and an Fe filter at 40 kV and 30 mA.

Thermogravimetric analysis (TGA)

All polymer samples were analyzed on thermal analyzer (TA Instruments, New Castle, DE, USA) and thermograms were obtained by heating about 5–7 mg of the polymer from ambient temperature to 700°C at 10°C/min. Weight loss of polymer against temperature was plotted to evaluate the thermal stability.

Differential scanning calorimetry (DSC)

The differential scanning calorimetry (DSC) thermograms were obtained on a DSC Quanta 100 Calorimeter (TA Instruments, New Castle, DE, USA). All the polymers (5 mg) were heated from ambient temperature to 300°C at 10°C/min. Second heating after quenching curve yielded T_g values.

Degradation and marker release studies

Degradation of polymer films and pellets fabricated by compression molding was attempted using weight loss as a measure of degradation. Quantitative evaluation was not easy since results were not reproducible due to interference by swelling at acidic pH and fragmentation at neutral and basic pH. Hence only qualitative observations were noted in 1*N* HCl buffer (pH 1.1), 1*M* Phosphate buffer (pH 7.4) and 1*M* sodium bicarbonate buffer (pH 10) respectively.

PNA release from all the polymer pellets was studied in phosphate buffer (pH 7.4) as reported earlier.[14] Briefly, 5 mg of PNA was mixed uniformly with 100 mg of polymer powder and pellets were prepared using compression force of 8 tons on KBr press at room temperature. The release of PNA was monitored using UV spectrophotometer (λ_{max} 380 nm).

Drug encapsulation in nanoparticles

PTX was loaded in DOCA based poly β amino ester nanoparticles by solvent diffusion precipitation (SD) and solvent evaporation precipitation (SE) method. In contrast to emulsion mediated nanoparticles preparation, solvent diffusion led precipitation does not need emulsifier since the solvent used is miscible with water. Since the polymers were charged, it prevented the aggregation of nanoparticles during preparation as confirmed by well dispersed and uniformly distributed nanoparticles in SEM images. Use of water immiscible solvents and emulsifiers was thus avoided as their removal from the final product is always incomplete and cumbersome.

I) Solvent diffusion precipitation method (SD)

Paclitaxel (15 mg) and DOCA based poly β amino esters (C_3C_{12}, C_3C_{24}, $C_{29}C_{30}$) (150 mg) were dissolved in 6 mL of THF. This solution was slowly added over a period of 15 min to 60 mL of chilled deionized water to yield PTX loaded nanoparticles. The residual THF was removed by rotary evaporation at room temperature and the solution was concentrated to 15 mL. These samples were filtered through 0.45 μ polyethersulfone (PES) disk filters (Acrodisc®, Pall Gellman) to remove unencapsulated PTX. The filtered solution was freeze dried to recover nanoparticles.

II) Solvent evaporation precipitation method (SE)

In this method 15 mg of PTX was dissolved along with 150 mg of DOCA based poly β amino esters (C_3C_{12}, C_3C_{26}, $C_{29}C_{30}$) in 60 mL of THF to which 15–20 mL of water was added over 15–20 min. The addition was continued till some opalescence developed. Thereafter THF was removed by rotary evaporation to yield nano suspension (Final volume 15 mL). The samples were centrifuged at 10000 rpm for 15 min. Supernatant was removed and particles were redispersed in fresh distilled water. This was repeated three times and then the particles were recovered by freeze drying.

Particle size and zeta potential determination

The particle size measurements of all the samples prepared by SD method were performed using a Brookhaven Instruments Corp. UK 90 Plus particle size analyzer at a fixed angle (θ) of 90°. Nanoparticles dispersions were prepared in double distilled water and filtered through a PES syringe filter (0.45μ, Acrodisc®, Pall Gellman). All the experiments were carried out at room temperature in triplicate at 1 mg/mL. Zeta potentials were measured by applying an electric field of 7.0 V/cm across two electrodes and providing inputs of pH and particle sizes. For each measurement 5 runs were averaged with each run employing 10 cycles for 3 min. Zeta pals software in Brookhaven instruments was used to analyze data.

Scanning electron microscopy (SEM)

All the particle dispersion samples prepared by SE method were imaged by drop casting method. The samples were dried on a stub and then coated with gold vapor. The samples were imaged on FEI Quanta 200—3D model, dual beam SEM (ESEM) with EDAX. The electron source was Tungsten filament. Resolution was 3 nm.

PTX content determination

5 mg of Paclitaxel loaded nanoparticles prepared by either method were weighed and 1 mL of THF was added to dissolve both polymer and PTX. Final volume was made up with ethanol. 25 μL of this volume was injected in HPLC to determine total drug content. The equipment used was an isocratic reverse-phase HPLC (Agilent 1100 series, Agilent Technologies, Wilmington, DE) with C_{18} column at 25°C and mobile phase acetonitrile–water (50 : 50 v/v) at a flow rate of 1.0 mL/min. PTX content was determined using calibration curve in the range 1–100 μg/mL and detection limit above 0.5 μg/mL.

PTX release studies

PTX loaded nanoparticles (10 mg) were added to release medium, i.e., 5 mL 1*M* sodium salicylate in phosphate buffered saline solution (PBS; pH 7.4) and loaded in the dialysis bag (molecular weight cut off 2000 Da) which was incubated at 37°C in 45 mL of release medium. The aliquots were withdrawn every 12 h and the same volume of fresh release medium held at the same temperature was replaced. The samples were assayed for PTX content by HPLC method using standard curve.

RESULTS AND DISCUSSION

Synthesis and characterization of Deoxycholyl diacrylate monomers

DOCA has a steroidal nucleus with two hydroxyls and one carboxylate functionality. Acid catalyzed esterification of DOCA with Methanol, Ethylene glycol and Trimethylolpropane yielded respective esters having two, three and four hydroxyl groups respectively. These esters were further used for the synthesis of Deoxycholyl ester diacrylates which were polymerized to yield poly β amino esters.

Deoxycholyl glycol diacrylate (DGDA)

This monomer was designed in such a way that steroidal moiety would be incorporated longitudinally in the backbone through polymerizing acrylate functionalities at the head and tail end of the monomer. C_{24} carboxyl group of DOCA was esterified with excess of Ethylene glycol to yield Deoxycholyl monoglycol ester. DG has three hydroxyl functionalities in which terminal hydroxyl group of ethylene glycol is primary while hydroxyl at $C_{3\alpha}$ position is secondary and oriented at axial position. On the contrary, the hydroxyl group at C_{12} is sterically hindered. Hence when acryloyl chloride is added in stoichiometric proportions to the solution of glycol ester of DOCA, reaction on these hydroxyls yields diacrylate esters as major product along with mono and triacrylate esters. Diacrylate ester was isolated by silica gel column chromatography using ethyl acetate and pet ether as eluent. The acrylate esterification of the hydroxyls at C_3 and C_{26} positions was demonstrated by ^{1}H-NMR and further confirmed by ^{13}C-NMR.

Methyl deoxycholate diacrylate (MDDA)

This monomer was designed in such a way that steroidal moiety would be incorporated transversely in the backbone through polymerizing acrylate functionalities at head and side end of the monomer. C_{24} carboxyl group of DOCA was esterified with excess methanol to yield methyl deoxycholate. MD has two hydroxyl functionalities, i.e., at $C_{3\alpha}$ and C_{12} positions. Addition of excess acryloyl chloride to the steroidal diol did not result in exclusive diacrylate formation, some monoacrylate always accompanied diacrylates. As mentioned earlier, acrylation is favored at C_3 position however C_{12} hydroxyl is sterically hindered and even 100% excess of acryloyl chloride could not result in complete conversion of hydroxyl on C_{12} to the acrylate ester. Diacrylate ester was isolated by purification on silica gel column chromatography using ethyl acetate and pet ether as eluent. The formation of acrylate esters of the

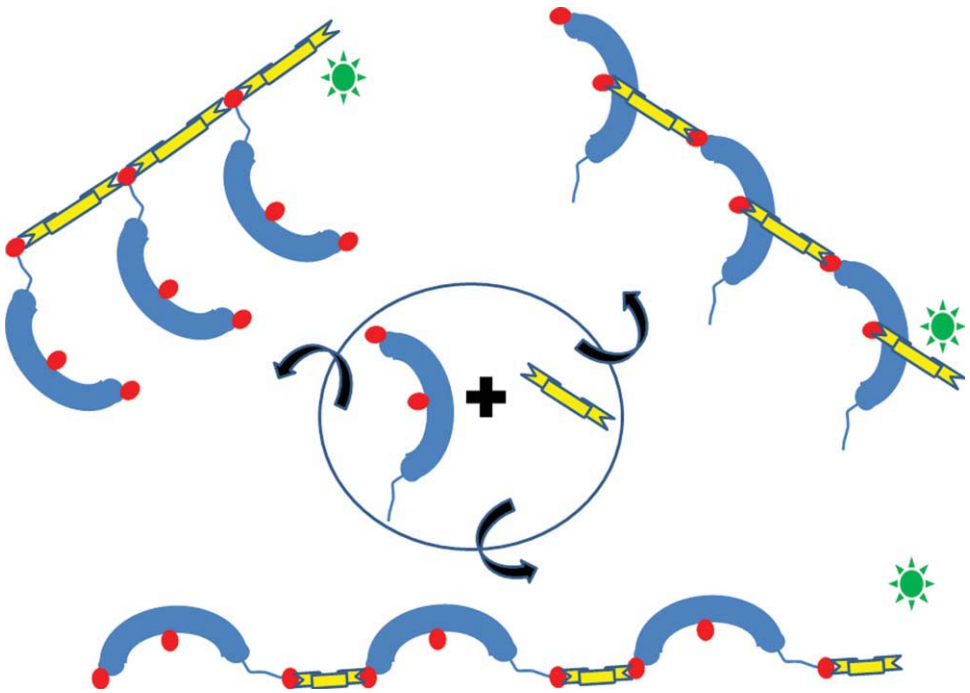


Figure 1 Schematic representation of DOCA polymerization in different structural planes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hydroxyls at C_3 and C_{12} positions was demonstrated by ^{1}H-NMR and further confirmed by ^{13}C-NMR.

Trimethylolpropane deoxycholate diacrylate (TMPDDA)

This monomer was designed in such a way that steroidal moiety would remain pendent to the backbone through polymerizing acrylate functionalities at the tail end of the monomer.

C_{24} carboxyl group of DOCA was esterified with excess TMP to yield TMP deoxycholate monoester. TMP deoxycholate has four hydroxyl functionalities of which two on TMP are primary while the other two on steroidal nucleus are secondary which are comparatively less reactive. Stoichiometric addition of acryloyl chloride to TMP deoxycholate solution favors reaction on primary hydroxyl groups but some reaction does take place on C_3 hydroxyl as well. This leads to the formation of triacrylate and monoacrylate esters as other side products. Diacrylate ester was isolated by silica gel column chromatography using ethyl acetate and pet ether as eluent. The acrylate esterification of the hydroxyls on Trimethylolpropane was demonstrated by ^{1}H-NMR and further confirmed by ^{13}C-NMR.

Synthesis and characterization of poly (Deoxycholyl TMDP β amino esters)

DOCA based monomers synthesized in earlier section were polymerized in different structural planes as head to tail, head to side and pendent through tail by $AlCl_3$ catalyzed Michael addition to yield novel poly (Deoxycholyl TMDP β amino esters) as described in details below (Fig. 1).

Michael addition reaction is reported to be extremely sluggish and take 5 days at 50°C for completion of polymerization reactions.[19–21] Lewis acids (e.g., $AlCl_3$) are known to accelerate electrophilic reactions in organic chemistry.[22–24] In the present case, $AlCl_3$ on addition to diacrylate solution formed coordinate complex with carbonyl oxygen of acrylate esters. Once this complex was formed the electronic resonance across ester bond resulted in the generation of stable electrophilic center at olefinic methylene which favored nucleophilic addition of amines. The rate of reaction was however limited by steric factors and increase in viscosity of medium during polymerization.

C_3 and C_{26} polyaddition [poly (DGDA-co-TMDP)]

In this approach, DGDA readily polymerizes with TMDP which acts as Michael donor on Deoxycholyl acrylate esters of hydroxyls at C_3 and C_{26} position and hence is referred to as C_3 and C_{26} polyaddition. Deoxycholate ester was polymerized in head to tail manner with the incorporation of steroidal moiety alternating with TMDP in the main polymer backbone. ^{1}H-NMR of the final product indicated decrease in peak of acrylates on Deoxycholate moiety which suggested Michael addition mediated polymerization.

In ^{13}C-NMR of polymer $CH{=}CH_2$ peaks in the range (125–135 δ) were not observed but peak at

53.69 δ ascribed to CH_2—NH of TMDP confirmed presence of TMDP along with Deoxycholate carbon peaks in the final polymer.

From the ^{1}H-NMR, polymer molecular weight was also determined using ratio of one proton on C_{17} methyl group to protons on diacrylate ester. In DG ratio of C_{17} proton to diacrylate was 1 : 6. Since the amine to diacrylate ratio used was 1, the resulting polymer can be expected to have acrylate at one end and amine at another end. Taking reference of any completely resolved peak of Deoxycholate unit and comparing it with terminal acrylate protons, degree of polymerization of polymers was determined. The ratio of three acrylate protons to single proton at C_{17} yields DP 15.96. Thus for every three terminal acrylate protons, 15.96 number of C_{17} proton were present, indicating presence of 15.96 Deoxycholate units in a polymer chain which suggest the molecular weight of polymer to be 11874. GPC analysis indicated M_w 2144 and M_n 563, PDI 3.8. The molecular weight determination by ^{1}H-NMR is absolute but complete resolution of Deoxycholate peaks for integration and interference of other impurities is difficult to overcome while the molecular weight determined by GPC is relative to polystyrene standards and is governed by the conformation of the chain which determine its hydrodynamic volume.

C_3 and C_{12} polyaddition [poly (MDDA-co-TMDP)]

MDDA was polymerized in head to side structural plane by Michael addition of TMDP on acrylates esters of hydroxyls at C_3 and C_{12} and hence referred to as C_3 and C_{12} polyaddition. The polymerization was confirmed from the presence of presence of TMDP peaks in final polymer using ^{1}H-NMR as discussed earlier.

In ^{13}C-NMR of the polymer, CH=CH_2 peaks in the range (125–135 δ) were not observed while peak at 53.72 δ ascribed to CH_2—NH of TMDP confirmed presence of TMDP in polymer along with Deoxycholate nucleus carbon peaks.

In ^{1}H-NMR MDDA ratio of C_{17} methyl proton to diacrylate was 1 : 6. On polymerization the ratio of three terminal acrylate protons to single C_{17} proton was found to be 3.4. Thus for every acrylate unit at terminal, 3.4 units of Deoxycholate units are present in chain indicating DP 3.4. The molecular weight calculated was found to be 2461. GPC analysis indicated M_w 2160 and M_n 1552, PDI 1.39.

C_{29} andC_{30} Polyaddition [poly (TMPDDA-co-TMDP)]

TMPDDA was polymerized as pendent by Michael addition of TMDP on acrylate esters of hydroxyls on TMPD designated as carbon 29 and 30 hence referred to as C_{29} andC_{30} Polyaddition. In this case Deoxycholate moiety is not part of polymer backbone which makes this polymer structurally different from the earlier two polymers. The polymerization was confirmed from the presence of TMDP peaks in the final product using ^{1}H-NMR as demonstrated in previous case.

In ^{13}C-NMR of the polymer, CH=CH_2 peaks in the range (125–135 δ) were not observed as in earlier cases and peak at 53.73 δ ascribed to CH_2—NH of TMDP was observed which confirmed presence of TMDP in polymer along with Deoxycholate nucleus carbon peaks.

In ^{1}H-NMR of TMPDDA, ratio of C_{17} proton to diacrylate was 1 : 6. On polymerization the ratio of three terminal acrylate protons to C_{17} single methyl proton was found to be 9.25 and hence DP 9.25. The molecular weight calculated was 7649. GPC analysis indicated M_w 9375 and M_n 5630, PDI 1.665.

Thus these three approaches yield Deoxycholate based polymers having molecular weight Mw 2000 to 9000 indicating the presence of oligomers containing 4 to 16 steroidal moieties in chains. Low molecular weight of these polymers can be ascribed to the steric hindrance caused by the bulky steroidal diacrylates towards polymerization.

FTIR spectroscopy

All poly (Deoxycholyl β amino esters) were characterized by IR spectroscopy. In poly (DGDA-*co*-TMDP) both the hydroxyls are utilized during polymerization step hence no peak is observed at 3541 cm^{-1}. In poly (MDDA-*co*-TMDP), one hydroxyl is free and another participates in polymerization. Hence a weak narrow peak is seen at 3541 cm^{-1}. The peak in the range 3400 to 3600 cm^{-1} which corresponds to free hydroxyls is observed in poly (TMPDDA-*co*-TMDP) at 3541 cm^{-1} wherein both the hydroxyls on Deoxycholate unit are free. Another peak at 3445 cm^{-1} can be observed in all oligomers which could be ascribed to β amino group. IR spectrum also exhibited weak peaks corresponding to acrylate esters at 1640 cm^{-1} present at the terminal position in all the oligomers (Fig. 2).

X-ray diffraction studies

DOCA based poly β amino esters were also characterized by XRD (Fig. 3). Crystallinity of poly (Deoxycholyl TMDP β amino esters) was investigated in the range 5–80°. Earlier reports indicated that the bile acid polymers because of their rigid steroidal structure and stacking ability formed crystalline polymers which were difficult to solubilize.[25] The polymers synthesized in this work exhibited a single

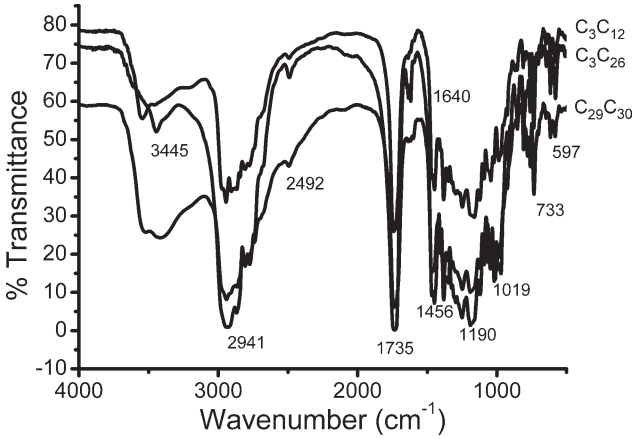


Figure 2 IR spectra of poly (Deoxycholyl TMDP β amino esters).

diffraction peak at 17.48° which confirmed that they are amorphous materials.

Thermogravimetric analysis

Thermogravimetric analysis (TGA) of all poly (Deoxycholyl TMDP β amino esters) were performed at heating rate of 10°C/min. All the polymers are highly thermostable and only 10% weight loss was observed up to 300°C. The weight loss was complete at 450°C as a result of decomposition and degradation (Fig. 4).

Differential scanning calorimetry studies

Differential scanning calorimetry (DSC) was performed at heating rate of 10°C/min in the temperature range −40 to 270°C. Glass transition T_g values for poly (DGDA-*co*-TMDP), poly (MDDA-*co*-TMDP) and poly (TMPDDA-*co*-TMDP) were 77.26, 71.19 and 86°C respectively, (Fig. 5). These values are comparable to T_g values of high molecular weight (M_n 18000) Lithocholic acid based polyanhydride homo-

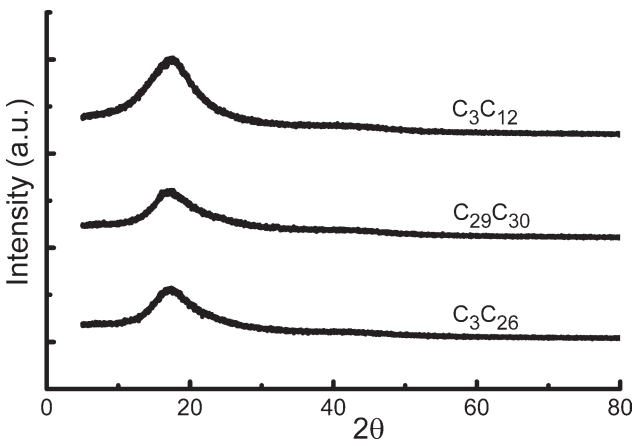


Figure 3 Powder X- ray diffractograms of poly (Deoxycholyl TMDP β amino esters).

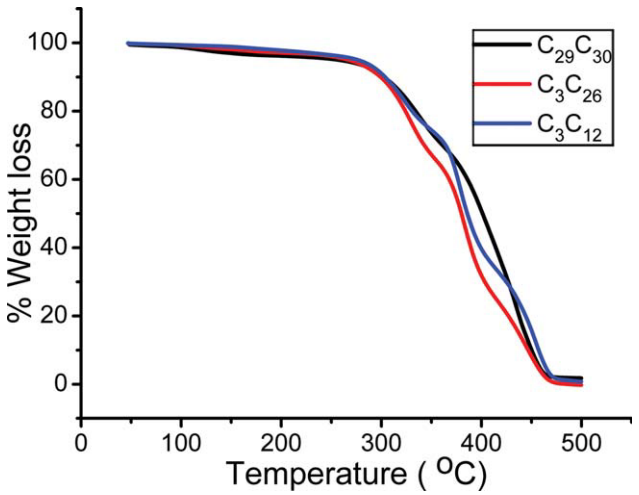


Figure 4 TGA curves of poly (Deoxycholyl TMDP β amino esters). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

polymer (T_g 85°C) and are higher than their copolymers with Sebacic acid (13°C).[14] However the values are lower than those for high molecular weight bile acid polymers (M_n 25000–75000, T_g 108–130°C) synthesized using click chemistry.[17]

Degradation and marker release studies

In general, poly (β amino ester) based on bile acid were expected to be highly hydrophobic because of the presence of Deoxycholate moieties. Sensitivity towards pH was observed in these polymers due to incorporation of amines in the main chain backbone. These polymers formed films by solvent evaporation method but they turned brittle and were broken into pieces when immersed in buffers. Hence compression molded pellets were prepared. Pellets collapsed and formed gelatinous mass at pH 1, while pellets at

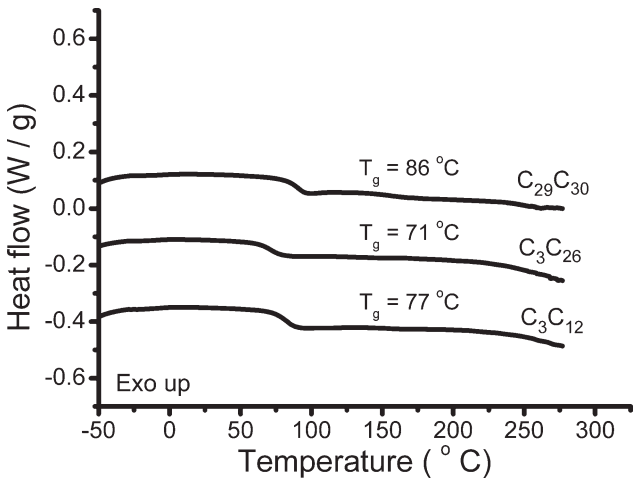


Figure 5 DSC thermograms of poly (Deoxycholyl TMDP β amino esters).

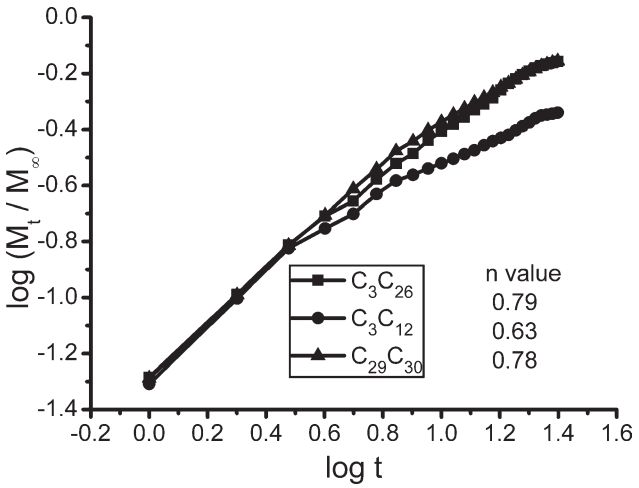


Figure 6 Mechanism of PNA release from poly (Deoxycholyl TMDP β amino esters) pellets.

pH 7.4 and 10 did not show any observable changes immediately. With time gelatinous mass decreased in size and finally turbid solution remained at pH 1 while in other samples, fragmentation of pellets increased with time. Qualitatively pellets disappeared in 15–20 days in pH 1 buffer and in 40–60 days fragmented in buffers at pH 7.4 and 10. Quantitative degradation study was not possible since pellets displayed abrupt weight changes even after removal, washing and drying. These pellets adsorbed buffer salts due to presence of amine in the backbone. Therefore the degradation could not be followed quantitatively by weight loss method.

PNA release was studied in phosphate buffer (pH 7.4) over a period of 1 month. Fraction of PNA released from the pellets was estimated with time using UV spectroscopy. Mechanism of PNA release from polymer matrix was be elucidated from Peppas equation[26–34]

$$M_t/M_\infty = k[t]^n \quad (1)$$

Where M_t and M_∞ are amounts of PNA released at time t and ∞, k is proportionality constant and n is an exponential constant.

When the release is governed by Fickian diffusion of the drug, $n = 0.5$.

As a special case when the drug release is controlled by the penetration of the medium and is followed by the swelling and or erosion of the polymer, $n = 1$.

When the diffusion is controlled by the relaxation in polymers, n varies in between 0.5 to 1. This is specifically the case for glassy polymers.[26–34] Plot of log M_t/M_∞ versus log t yielded slope (n) in the range 0.6–0.8 (Fig. 6). It may be noted that all the polymers used in this work are glassy under release conditions. Thus PNA release followed anomalous release kinetics.

Preparation and characterization of PTX-loaded nanoparticles

SD and SE techniques were employed for the preparation of PTX loaded nanoparticles. In first method, precipitation of polymer along with PTX takes place instantaneously. In the later case, PTX and polymer were dissolved in large volume of solvent and water was added as non solvent in small amounts. Thereafter the solvent was removed at a constant pressure which led to slow precipitation of the polymer and PTX in water yielding PTX loaded nanoparticles. This method has been explored by researchers for the preparation of liposomes and polymersomes[35] and we were keen to apply it for preparation of nanospheres for studying effect of method of preparation on morphology, size and drug loading.

Nanoparticles prepared by SD method were too small to be imaged by SEM. The particle size of these nanoparticles in dispersion measured by Brookhaven particle size analyzer at 90° was in the range 75–270 nm as shown in Table I. Poly (DGDA-*co*-TMDP) and poly (TMPDDA-*co*-TMDP) yielded smaller nanoparticles compared to those obtained from poly (MDDA-*co*-TMDP).

SE method yielded particles which were larger than those obtained by SD method but they were spherical and uniform with size in the range 0.4–1 μm as observed by SEM (Fig. 7). Further optimization of size could be achieved by controlling rate of addition of water, evaporation of solvent and concentration of polymer in solvent.

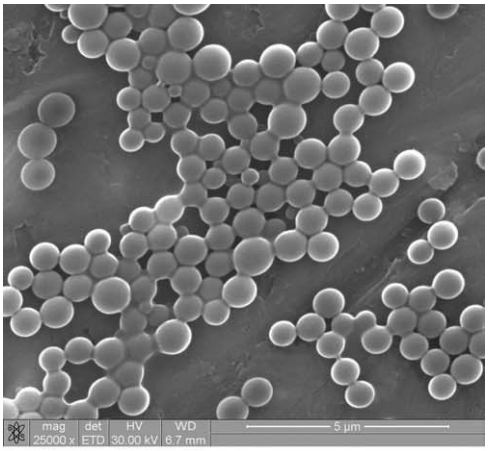
All PTX loaded nanoparticles exhibited positive zeta potential values in the range 37–45 mV, which indicated that nanoparticles were stable and cationic in nature. The cationic nature can be attributed to β amino ester linkage present between DOCA units.

Drug loading and release from nanoparticles

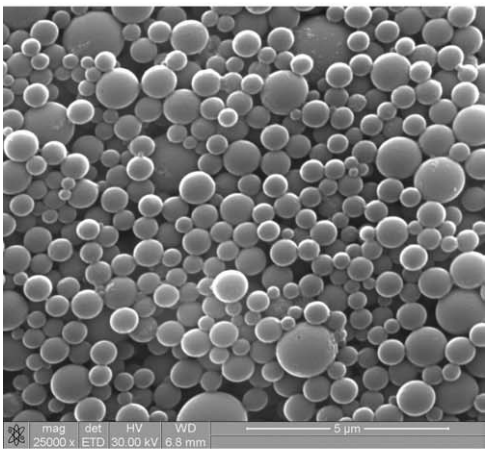
PTX is a highly hydrophobic molecule hence can be expected to exhibit affinity towards hydrophobic steroidal part of DOCA. Hence different DOCA based poly (β amino esters) were synthesized and also explored for the encapsulation of PTX. Drug content analysis indicated that 50–95% PTX was loaded in nanoparticles. PTX loading was greater in case of nanoparticles prepared by SE method (Table II).

TABLE I
Particle Size and Zeta Potential of PTX-Loaded Poly (Deoxycholyl TMDP β Amino Esters) Nanoparticles

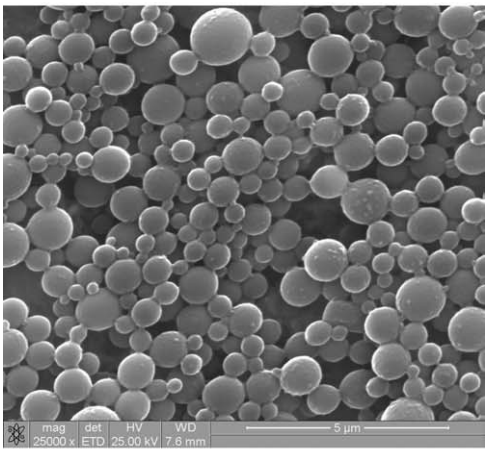
Polymer type	Effective diameter (nm)	polydispsersity	Zeta potential (ξ) (mV)
C_3C_{26}	118	0.156	37.52
C_3C_{12}	267	0.226	42.39
$C_{29}C_{30}$	76	0.230	45.26



(a)



(b)



(c)

Figure 7 SEM micrograph of PTX loaded nanoparticles of poly (Deoxycholyl TMDP β amino esters) (a) C_3 C_{26}, (b) C_3 C_{12}, (c) C_{29} C_{30}.

Nanoparticles prepared by SD method using poly (DGDA-*co*-TMDP) (SD1), poly (MDDA-*co*-TMDP) (SD2) and poly (TMPDDA-*co*-TMDP) (SD3) were filtered through 0.45 μ filters to remove larger aggregates and precipitated PTX. Nanoparticles prepared by SE method using poly (DGDA-*co*-TMDP) (SE1), poly (MDDA-*co*-TMDP) (SE2) and poly (TMPDDA-*co*-TMDP) (SE3) were larger in size hence centrifuged, resuspended in water and centrifuged again to remove traces of solvent and unentrapped soluble PTX in the medium. The particles prepared by SE method were imaged using SEM. The images did not show presence of free PTX crystals which confirmed that PTX was entrapped within the nanoparticles. PTX if not encapsulated has been reported to precipitate in water or buffer as angular or needle crystals.[23] Imaging of formulations for PTX crystals is a standard method for the determination of instability of Paclitaxel encapsulated formulation.[24] In SD method PTX loading was found to be lower. This could be due to the removal of PTX loaded larger nanoparticles or their aggregates during filtration step, which reduced final drug loading in the samples.

TABLE II
PTX Content in Poly (Deoxycholyl TMDP β Amino Esters) Nanoparticles

Preparation method/polymer	% PTX loading
SD1	58.78
SD2	48.76
SD3	66.46
SE1	97.28
SE2	99.23
SE3	92.26

Nanoparticles prepared by SD method using poly (DGDA-*co*-TMDP) released 57% of encapsulated PTX within 96 h. In contrast, nanoparticles prepared by SE method using poly (MDDA-*co*-TMDP) oligomers released 25% of PTX in the same time interval (Fig. 8). All the nanoparticles prepared by both the methods using other oligomers released PTX within

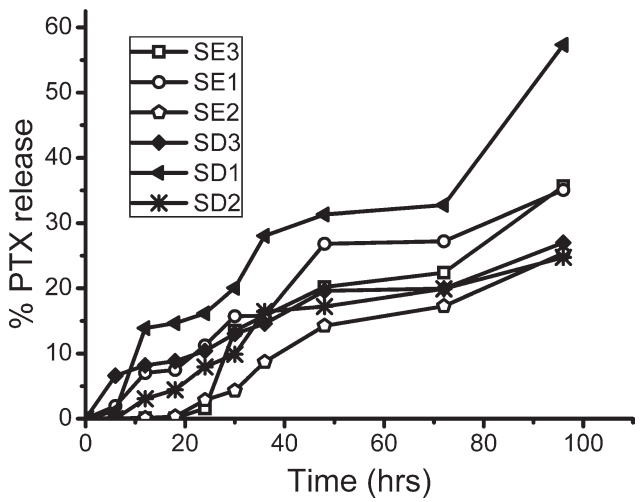


Figure 8 PTX release from nanoparticles prepared from poly (Deoxycholyl TMDP β amino esters) by solvent evaporation (SE) and solvent diffusion (SD) methods.

the range of 25–57%. The release patterns were thus dependent on numerous factors like type of polymer and their degradation, extent of hydrophobic interactions of PTX inside nanoparticles and method of preparation of nanoparticles.

CONCLUSIONS

Deoxycholate ester diacrylates were synthesized in three different structural planes using different hydroxyl groups at C_3, C_{12} and C_{26} and characterized using ^1H, ^{13}C-NMR and IR spectroscopy. The monomers were polymerized by 1, 4 Michael addition of TMDP catalyzed by $AlCl_3$. Poly (Deoxycholyl TMDP β amino esters) were mostly oligomeric, amorphous in nature and highly thermostable with T_g in the range 70–80°C. Polymer degradation was very slow at basic and neutral pH but was fast in acidic conditions. PNA release from the pellets of poly (Deoxycholyl TMDP β amino esters) was diffusion controlled but followed anomalous release kinetics. PTX loaded nanoparticles prepared by SE method were in the range 0.4–1 μ as indicated by SEM. SD method yielded PTX loaded nanospheres of size 75–265 nm as determined by particle size measurements. PTX encapsulation efficiency was in the range 50–95%. Release in 1*M* sodium salicylate phosphate buffer (pH 7.4) indicated that 55% of PTX was released over 96 h from these nanoparticles. The positive charge, high hydrophobicity and bile acid backbone of these oligomeric materials makes them very useful in designing carriers for gene delivery and oral transmucosal delivery of proteins and anticancer drugs.

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