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Research Article

Controlled release of 5-Fluorouracil by a novel L-Lysine based polyesterurethane material synthesized from Epoxide and CO_2 via a novel dicopper salen catalyst

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Abstract

Controlled release of anticancer drug 5-Fluorouracil by several delivery systems are known including porous polymeric materials. Herein we report a novel L-lysine based porous polyesterurethane material 1 which acts as a controlled release vehicle for 5-Fluorouracil. Polyesterurethane material 1 was synthesized from a green isocyanate and phosgene free synthetic route involving conversion of epoxide 2-(phenoxymethyl)oxirane and CO_2 to cyclic carbonate 2 followed by ring opening with an amino acid L-Lysine to a bishydroxy compound 3 under green aqueous reaction condition. The bishydroxy compound 3 was subsequently reacted with 0.66 equivalent of trimesyl chloride in presence of triethyl amine to get the polyesterurethane material 1. The polyesterurethane material 1 was characterized via NMR, IR and MALDI analysis. From the SEM image of the polyesterurethane 1 and 5-Fluorouracil encapsulated polyesterurethane 1 it is evident that material 1 remain with porous topology which is filled by 5-Fluorouracil that is further evidenced by EDX spectroscopy with the presence of Fluorine. The controlled release of 5-Fluorouracil from the drug encapsulated 1 was monitored via UV visible spectroscopy at pH 7.4.

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Cancer is the second most common disease which responsible for deaths all over the world. Therefore, treatments of cancer offer a huge challenge. Many medications are available for cancer treatment [1-6], among this 5-flurouracil plays a major role by exerting its anticancer effects through inhibition of thymidylate synthase (TS) and incorporation of its metabolites into RNA and DNA. Although 5-flurouracil is an established anticancer drug for colon cancer, esophageal cancer, stomach cancer, pancreatic cancer, breast cancer, and cervical cancer [7-10]. but in order to increase its efficacy several nanodrug delivery system has been explored for transporting anti-cancer drugs to colorectal cancer cells, while reducing undesired drug distribution in healthy tissues. CO_2 can be converted different value added materials [11,12] and among which conversion of epoxides to cyclic carbonates are well known [13-15]. Global warming is considered to be a serious challenge in the perspective of the earth's habitable climate conditions for which increasing rate of CO_2 emission is one of the main causes. Conversion of CO_2 to value added materials happened to be the main way out for reducing the

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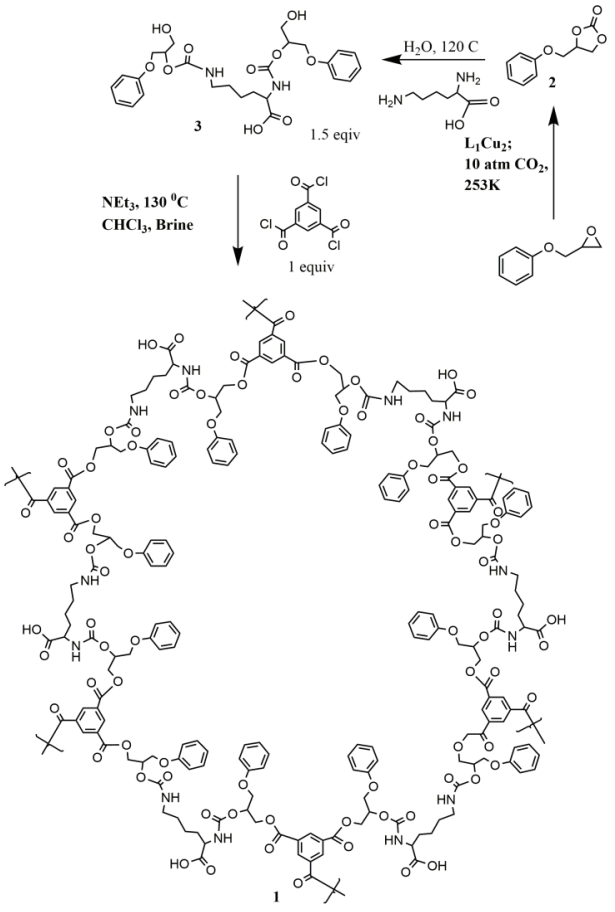
rate of CO_2 emission. Many reports of conversion of CO_2 to value added materials are known [16] among which conversion of epoxides to cyclic carbonates are well known [16-21]. Cyclic carbonates can be utilized for different purposes including the production of polyurethane and polyesterurethane materials [16-21]. Polyesterurethane materials from biobased substrates are important for their versatile applications as biodegradable materials in bone tissue engineering as well as hydrogels for drug delivery and in biomedicine [22-25]. These biobased polyesterurethane materials are widely synthesized from respective diols and diisocyanates [26-28]. Diisocyanate precursors are prepared from the diamines in presence of phosgene [29]. Organic isocyanates are very toxic for the human health which was proved during Bhopal gas disaster and phosgene is also considered to be highly toxic as 50 ppm exposure may cause lethal reaction in humans. In order to avoid the involvement of diisocyanates and phosgene for the production of polyesterurethane materials an alternative procedure has been discovered where ring opening of a cyclic-carbonate in presence of diamines give the respective bishydroxy compound which then undergo copolymerization with the acid chlorides to generate the polyesterurethane materials [30,31]. Here we have first successfully synthesized the ringopened bishydroxy compound 3 by reacting the monocyclic carbonate 4-(phenoxymethyl)-1, 3-dioxolan-2-one (2) with the amino acid L-Lysine in presence of water at 120°C (Scheme 1). The ring opened diol 3 was converted into polyesterurethane material 1 by reacting it with trimesyl chloride in 3: 2 rations in presence of triethyl amine as shown in Scheme 1.



Scheme 1: Synthesis of the polyesterurethane material 1 from L-lysine and cyclic carbonate 2.

Although there are reports of several [32], polyurathene based material used as control drug release vehicle but there is no report of polyesterurethane material generated from amino acid which is considered to be a very promising candidate for the development of drug release vehicles as it has been done in our present work. Hence the crosslink polymeric network which has been synthesized from amino acid L-lysine and working as a very good drug vehicle for anti-cancer drug 5-fluorouracil can be considered as a novel route for the delivery of drug material based on polymeric networks designed from bioactive materials.

The synthesis of cyclic carbonate 2 was achieved by conversion of epoxide 2-(phenoxymethyl)oxirane in presence of CO_2 using an efficient novel supramolecular rectangular bis salen dicopper complex heterogeneous catalyst L_1Cu_2 . Salen based catalysts with different metallic systems have been widely used for the catalysis of the cyclic carbonates but the copper based salens have been rarely used for this purpose [33]. As copper salts are commercially readily available and cheap hence the use of copper based catalysts in the cyclic carbonate synthesis would be interesting. The synthesis of the novel copper based catalyst L_1Cu_2 was performed according to the synthetic Scheme 2 with the final catalyst being characterized clearly by MALDI as well as elemental analysis. The MALDI spectra of the copper complex L_1Cu_2 shows the molecular ion peak as $[M]^+$ at 1200.0792 with respect to the expected mass at 1200.1753 (Figure S4). The free salen ligand L_1 was also detected in the MALDI spectra at 1076.1738. The reaction of the salicylaldehyde proligand L with orthophenylene diamine in 1:1 ratio in presence of two equivalent of copper acetate generates the catalyst L_1Cu_2. The salicylaldehyde proligand L was synthesized by the reaction of protected 5-bromo-2-hydroxybenzaldehyde with 1,8 diethynyl anthracene in 2:1 ratio as shown in Scheme 2.

The salicylaldehyde proligand L was fully characterized by NMR and ESI MS studies. In the proton NMR spectra the peak at 10.13 ppm corresponds to the aldehyde proton whereas in ^{13}C NMR spectra the carbonyl carbon appears at 190.93 ppm (Figure S1 and Figure S2). The ESI MS in negative mode gives the [M-H]- peak at 465.0635 as compared to the expected peak at 465.1127. (Figure S3).

Cyclic carbonate 2 was synthesized by reaction of the epoxide 2-(phenoxymethyl)oxirane with CO_2 at 10 atmospheric pressure and 80 degrees centigrade in a high pressure steel reactor in 95% yield (Scheme1). The reaction was carried out without any solvent and the catalyst L_1Cu_2 was used in 0.062 mol% along with cocatalyst tetrabutyl ammonium bromide 0.23 mol% for the purpose with turnover number more than 1200. The catalytic efficiency of the novel copper salen complex is quite promising as compared to the previously reported salen based catalysts for the conversion of epoxides to cyclic carbonates [34] with the aluminium disalen complex showing the highest turnover number 1027 with 1 mol% of catalyst and cocatayst loading [25]. It has been found previously that the

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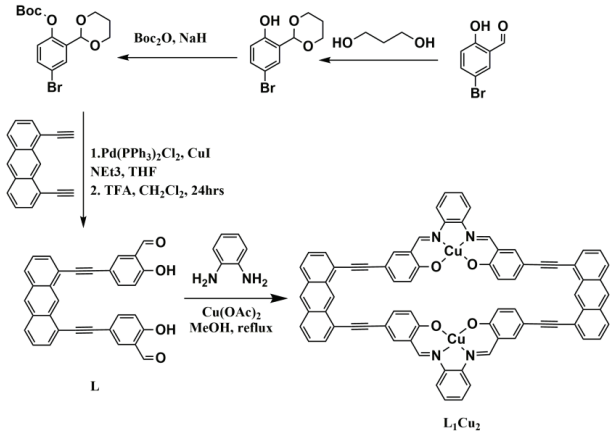

Scheme 2: Synthesis of the copper salen catalyst L1Cu$_2$ for the synthesis of cyclic carbonate 3 from CO_2 and epoxide 2-(phenoxymethyl)oxirane.

dinuclear salen complexes [35] have better efficiency than the mononuclear salen complexes in the synthesis of cyclic carbonate from epoxide and CO_2. The mechanistic detail given by North et.al [36] shows that the dinuclear salen complexes acts simultaneously by binding both the epoxide and CO_2 and bringing them in close proximity for the conversion of cyclic carbonates. Based on this we try to designed our dinuclear salen catalyst where both the metal active sites can simultaneously bind the epoxide and CO_2 and increase the possibility of formation of cyclic carbonate by many fold which is reflected in our case in higher turn over number in formation of cyclic carbonates as compared to the mononuclear salen complexes or conventional catalyst such as Li salt which can provide only one metal active site per catalyst molecules. The formation of the cyclic carbonate 2 was initially indicated by the IR spectroscopy with the characteristic carbonyl stretching frequency corresponding to the cyclic carbonate appearing at 1793 cm^{-1} (Figure S6). The ^{13}C NMR shows the carbonyl carbon peak at 155 ppm corresponding to the cyclic carbonate 2 whereas the proton NMR spectra shows the complete disappearance of the peaks between 3.2 – 2.6 ppm marking the conversion of the epoxide to the corresponding dicyclic carbonate 2 (Figure S7). Very few reports are there for the ring opening of the cyclic carbonates by the bioactive amino acid in presence of water [37]. For the best of our knowledge this is the first example of the ring opening of a monocyclic carbonate by a diamino acid L-Lysine under green aqueous reaction condition. The product 3 was fully characterized via NMR as well as mass spectrometry. Novel porous polyesterurethane polymer 1 was synthesized by reacting ring opened diol 3 and trimesyl chloride in 3: 2 ratio at 130 °C in presence of triethyl amine. Compound 1 was isolated from the reaction mixture by successive washing with chloroform and brine solution. Compound 1 was initially characterized by proton NMR where the single peak at 8.6 ppm corresponds to the trimesyl protons and also comparing the proton NMR of the ring opened diol 3 with that of polymer 1 it is evident that compound 1 possesses a symmetrical structure. IR spectra of the (Figure S18) polymer compound 1 shows the peak at 1689 , 1222, 2852 and 2915 cm^{-1} which is comparable to standard polyesterurethane material [21,38]. The MALDI mass of compound 1 shows a typical polymeric nature with successive difference between two peaks corresponding to the successive expulsion of CH_2 or NH_2 groups respectively from the polymeric backbone (Figure S19). The TGA data of the polymer 1 shows initial mass loss of 8.47% at 70 °C corresponding to the expulsion of solvent from the material (Figure S20). Although there are several porous organic polymers [39-42] and polyurethane [43-46] based polymers have been reported for controlled drug delivery till date there are no report based on the amino acid containing polyesterurethane material Figure 1.

SEM image of 1 as shown in figure1 clearly indicates the formation of the porous polymeric network as proposed in Scheme1. The pour size distribution was performed from the respective SEM images where it shows the average pour size distribution for the crosslink polymeric network between 0.1 – 0.6 µm as shown in Figure S23. 5- Fluorouracil is a well known drug for colon cancer, esophageal cancer, stomach cancer, pancreatic cancer, breast cancer, and cervical cancer. In order to improve the therapeutic effect of this drug the controlled release of 5 fluorouracil is very important. To achieve the controlled release of 5 fluorouracil first the successful encapsulation inside the porous network of the polymer 1 was attempted by stirring the polymer 1 in the respective aqueous solutions of the 5- fluorouracil for approximately 5 hours at room temperature. The encapsulation was initially monitored via SEM imaging studies. The EDX spectra of the SEM image conclusively proves the dispersion of the drug molecules inside the porous polymeric network of 1 (Figure S22 and S24) by the appearance of the fluorine in the drug encapsulated SEM image of the polymer 1 whereas the EDX spectra of the pure polymer do not show any peak corresponding to fluorine. The IR data of the encapsulated polymer 1 (Figure S21) shows the retention of the polyesterurethane material after encapsulation.

The NMR data recorded in DMSO-d_6 of the 5-flurouracil encapsulated polymeric network clearly reveals the encapsulation of 5-flurouracil in the polymeric network in both proton and C13 NMR displaying slight upfield shift of the trimesyl proton in the proton NMR of the 5-fluorouarcil encapsulated polymer with resprct to polymer 1 as shown in S16 and S17. We propose that the upfield shift of the trimesyl proton could be due to the interaction between polymer 1 and encapsulated drug 5-fluorouracil. The proton NMR spectra of encapsulated 5-fluorouracil polymeric network also show the encapsulation of approximately 3 5-flurouracil unit per polymeric network unit as stated from the proton NMR integration ratios in Figure S15.

The controlled release of the 5-fluorouracil drug was monitored via UV vis spectroscopic studies using the drug encapsulated polymer 1 in phosphate buffer at pH 7.4 and taking out the aliquots solutions for UV measurement at certain time intervals. As represented in Figure 2 the drug release kinetics showed 80% of the drug being released within 4 hours.

Conclusion

We have synthesized the porous polyesterurethane polymeric material 1 via ring opening of a cyclic carbonate by aminoacid L-Lysine. Polymer 1 was characterized by IR, NMR as well as MALDI analysis whereas the porous texture of the

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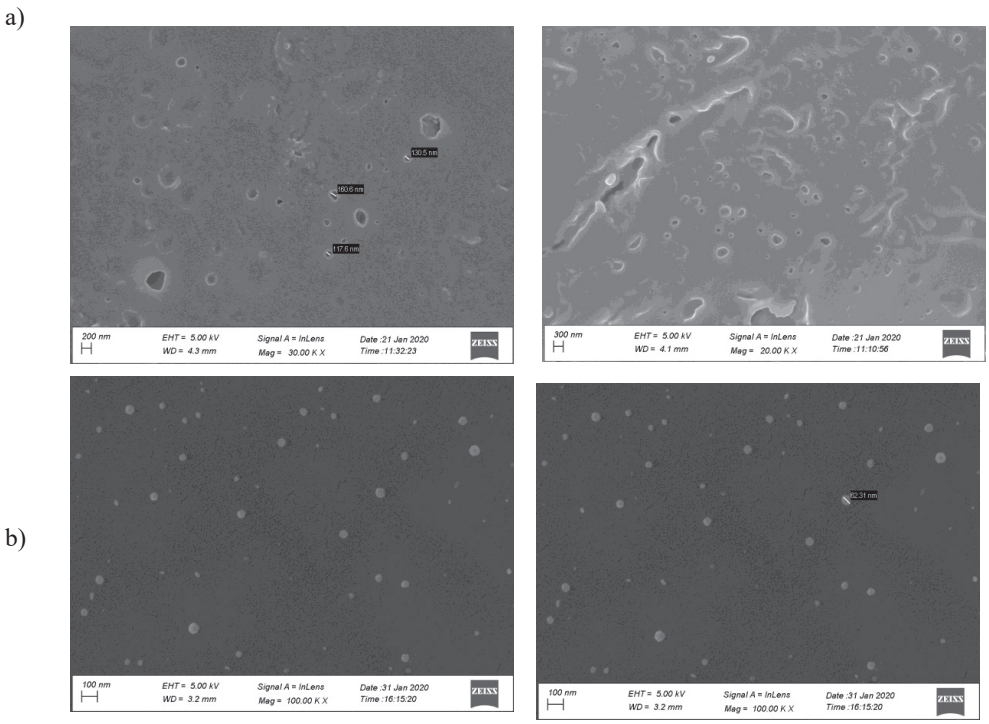

Figure 1: SEM image of the polyesterurethane polymer 1 (a) and polyesterurethane polymer 1 after encapsulation of the 5 fluorouracil drug (b).

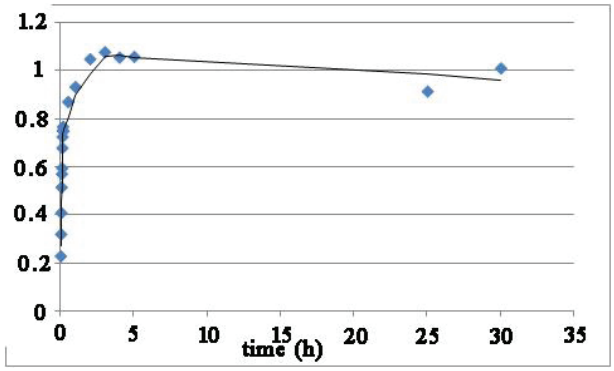

Figure 2: Controlled release of 5-Fluorouracil from the 5 Fluorouracil -polyesterurethane 1 composite. (Y-axis represent the concentration of the 5 Fluorouracil in the buffer solution at pH 7.4 in terms of optical absorption whereas X-axis represents the time interval).

material was observed in SEM. The cyclic carbonate synthesis was achieved by a novel supramolecular dicopper salen catalyst from the respective epoxide and carbon dioxide in high yield under heterogeneous reaction conditions. The ring opening of the cyclic carbonate was performed under green aqueous conditions to obtain a novel dihydroxo compound 3. The anticancer drug 5 fluorouracil was successfully encapsulated inside the porous polymer 1 which was evident from the FESEM analysis. The drug-polymer composite showed the controlled release kinetics of the drug 5 fluorouracil under 7.4 pH. This is the first example of an amino acid based polyesterurethane material being found to have potential for a controlled delivery vehicle for 5 fluorouracil.

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(Suplementary-Figures S1-S24)

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