Designing of Poly(l-lactide)—Nicotine Conjugates: Mechanistic and Kinetic Studies and Thermal Release Behavior of Nicotine

Medha Mili, Arvind Gupta, Monika, and Vimal Katiyar*  

Department of Chemical Engineering, Indian Institute of Technology Guwahati, Kamrup, Guwahati 781 039, Assam, India

ABSTRACT: The current work focuses on the ring-opening polymerization (ROP) of l-lactide (LLA) using N-heterocyclic functionalized molecules as an initiator for the synthesis of metal-free poly(l-lactide) (PLLA) conjugates. With this motivation, we have used a drug molecule, nicotine, having N-heterocyclic functionality as the initiator for the synthesis of PLLA conjugates. Structural characterizations carried out using matrix-assisted laser desorption ionization time-of-flight mass spectrometry, Fourier transform infrared, and NMR establish the reacting species during polymerization in the absence of any side reactions. However, side reactions occurred because of the absence of steric hindrance when polymerization is initiated using nicotine in the presence of benzyl alcohol. Accordingly, we report here a detailed investigation on the mechanism of nicotine as an initiator and propose an anionic-based mechanism for the ROP of LLA. Studies on the kinetics parameters have been performed for the nicotine-initiated ROP of LLA and have found that polymerization proceeds with a first-order dependence on both the monomer and initiator concentrations with a low activation energy of 4.9 kcal·mol⁻¹. Further, thermal release studies performed by hyphenated thermogravimetric—Fourier transform infrared analysis found that nicotine is released along with reduced toxins from these synthesized PLLA—nicotine conjugates. Thus, these PLLA—nicotine conjugates can in turn open up a new era in tobacco industries for the preparation of synthetic cigarettes and also in biomedical applications for drug delivery purposes. Herein, a few preliminary experiments using another drug molecule, nicorandil, having similar N-heterocyclic functionality were also conducted to support the role of nicotine as an initiator for the synthesis of PLLA conjugates.

INTRODUCTION

In recent years, the worldwide interest in biobased polymers is greatly increasing, and they are being studied intensively because of their ability to become a feasible alternative to petroleum-derived plastics in various applications. Amongst various biobased polymers available, polylactide [PLA], at present, is one of the most promising polymers. PLA belongs mainly to the aliphatic polyester family, commonly made from α-hydroxy carboxylic acids having enormous applications because of its tuneable biodegradability, nontoxicity, and biocompatibility. PLA has found applications in various areas such as food packaging, textile industries, and mainly in biomedical applications such as drug delivery, orthopedic fixation devices, and sutures, and so forth. Keeping in view its increasing applications, there has been a lot of advancement in the field of PLA synthesis. Synthesis of PLA can be carried out either in solution or in bulk. However, bulk polymerization is a more favorable technique for the production of PLA on a mass scale, as the rate of polymerization is faster as compared to solution polymerization and thus, we have focussed our investigations on the ring-opening polymerization (ROP) of l-lactide (LLA) in bulk. Numerous methods have already been exploited for the synthesis of PLA in bulk which includes direct polycondensation, azetropic-dehydrative condensation, melt/solid polycondensation, and ROP. Among the above synthesis methods, only bulk ROP has the potential to yield PLA with a high molecular weight within a short polymerization time and thus is the most preferred technique. Organometallic molecules including transition metal complexes of tin, zinc, yttrium, and so forth are widely explored as catalysts for PLA synthesis. Of the various metallic catalysts available, stannous octoate is the most widely used organometallic catalyst because of its high catalytic activity and also because it was approved by the American Food and Drug Administration (FDA) for food and biomedical applications. However, the use of metallic catalysts leaves traces of metals in the final polymeric product, which may pose undesirable problems for their use in medical applications. Keeping this in view, over the last few years, there has been a resurgence of interest in organocatalysts as a powerful metal-free alternative to organometallic catalysts. With this motivation, we have focussed our investigations purely on organic molecules based on N-heterocyclic functionality as initiators for PLA synthesis. The utilization of N-heterocyclic carbenes (NHC),
idine (DMAP),38 and phosphines39 acting as effective organo-
catalysts to promote lactide polymerization, to synthesize homo
and copolymers has been reported in literature.6,37,40–42

Herein, we have explored the initiation of LLA using the N-
heterocyclic molecule, nicotine, to synthesize poly( l-lactide-
(PLLA)—nicotine conjugates. Investigations utilizing a set of
N-heterocyclic functionalized molecules consisting of 4-
pyrrolidino-pyridine, pyridine, pyrrole, 2-methyl-pyridine, and
imidazole, which can effectively initiate the LLA molecules to
synthesize PLA,43 are already available in literature.

In this work, we have successfully synthesized in situ PLLA
conjugates under solvent-free bulk conditions having low
molecular weight (∼19 000 Da) as desired. We also carried
out polymerization reactions in the presence of a coinitiator
such as benzyl alcohol (BA) and observed the occurrence of
undesirable side reactions such as backbiting and cyclization
under these conditions. Accordingly, we have proposed the
mechanism of this N-heterocyclic molecule, nicotine, as the
initiator both in the presence and absence of BA and have also
determined the kinetics parameters. The hyphenated thermo-
gavimetric—Fourier transform infrared (TG—FTIR) technique
is used to investigate the thermal release behavior of the
synthesized PLLA conjugates. This technique is most widely
used to detect the volatile species released during thermal
degradation.44 Herein, we also present some preliminary
experimental results obtained using another N-heterocyclic
drug molecule, nicorandil, resulting in the synthesis of PLLA—
nicorandil conjugates.

## RESULTS AND DISCUSSION

In a series of experiments, ROP of LLA has been carried out
using nicotine as an initiator for PLA synthesis. Table 1 reports
the overall data obtained from our experiments which examine
the behaviour of the initiator, both in the presence and absence
of a coinitiator such as BA. In addition, we report the ROP of
LLA using nicorandil without using BA at the optimized
condition at which the maximum molecular weight is obtained.
It is noteworthy to mention that gel permeation chromatog-
raphs show a unimodel distribution which is in line with the
polymer \(M_n\) distribution that should be obtained during
addition polymerization.

### MALDI-TOF-MS Analysis

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) analysis of the synthesized PLLA conjugate samples has been performed. The resultant spectra are used to investigate the species taking part during the ROP of LLA using nicotine as an initiator and for the determination of the end groups attached with the grown PLLA chains. PLLA synthesized via the ROP of LLA by nicotine, nicotine + BA, and nicorandil having different end groups or formation of macrocycles are represented in eqs i–vi.

\[
M' = 72x + M_{nicotine}(162) + M_{Na}-(23) + M_{Li}^+(7) \quad (i)
\]

\[
M^2 = 72x + M_{nicotine}(162) + M_{K}^-(39) + M_{Li}^+(7) \quad (ii)
\]

\[
M^3 = 72x + M_{nicotine}(162) + M_{Na}^+(23) \quad (iii)
\]

\[
M^4 = 72x + M_{BA}(108) + M_{Na}^+(23) + M_{Li}^+(1) \quad (iv)
\]

\[
M^5 = 72x \quad (v)
\]

\[
M^6 = 72x + M_{nicorandil}(211) + M_{Na}^+(23) + M_{Li}^+(1) \quad (vi)
\]

where \(M'\), \(M^2\), and \(M^3\) represent the masses of PLLA chains
bearing nicotine, \(M^4\) represents the masses of PLLA chains
bearing BA, \(M^5\) is for PLLA, and \(M^6\) represents the masses of
PLLA chains bearing nicorandil as end groups. The term “x”
denotes the number of lactyl repeat units having an \(M_n\) value of
72 Da each. \(M_{Li}^+(7)\), \(M_{Na}^+(23)\), and \(M_{K}^-(39)\) are the
molecular weights of sodium ion, potassium ion, and lithium
ion, respectively, attached with the PLLA chains.

MALDI-TOF-MS spectra of PLLA conjugates synthesized
using nicotine are shown in Figure 1. The spectra clearly show
that PLLA synthesized by nicotine contains two varied types of
chains, obtained at masses, in consistent with the above two
equations (eqs i and ii) and hence confirm the occurrence of
nicotine at the terminal end of each PLLA chain.

PLLA conjugates synthesized using nicotine in the presence
of BA (Figure 2) consist of three varied types of PLLA chains
having masses corresponding to eqs iii–v. These PLLA chains
can be considered as four different envelopes A, B, C, and D.
Envelope A refers to the PLLA chain having a nicotine terminal
with masses at an interval of 144 Da, similar to that in Figure 1

### Table 1. Experimental Results of the ROP of LLA Using Nicotine and Nicorandil as Initiators

| run | initiator/[L]/[I] | T (°C) | time (h) | \(M_n\) (g/mol) | \(M_w\) (g/mol) | PDF | conv. (%) |
|-----|----------------|--------|----------|----------------|----------------|-----|-----------|
| 1   | nicotine-50    | 160    | 12       | 3100           | 8200           | 2.6 | 97        |
| 2   | nicotine-50    | 160    | 24       | 5800           | 16 300         | 2.8 | 98        |
| 3   | nicotine-50    | 160    | 36       | 6900           | 18 700         | 2.7 | 99        |
| 4   | nicotine-50    | 160    | 48       | 6600           | 18 000         | 2.7 | 98        |
| 5   | nicotine-50    | 120    | 36       | 5400           | 15 700         | 2.9 | 85        |
| 6   | nicotine-50    | 140    | 36       | 6500           | 18 000         | 2.7 | 91        |
| 7   | nicotine-50    | 180    | 36       | 3600           | 10 400         | 2.8 | 98        |
| 8   | nicotine-100   | 160    | 36       | 6800           | 17 600         | 2.6 | 98        |
| 9   | nicotine-150   | 160    | 36       | 6700           | 16 400         | 2.5 | 95        |
| 10  | nicotine-250   | 160    | 36       | 6200           | 14 900         | 2.4 | 80        |
| 11  | nicotine-500   | 160    | 36       | 4400           | 9800           | 2.2 | 75        |
| 12  | nicotine/BA-50 | 160    | 12       | 2000           | 3800           | 1.9 | 98        |
| 13  | nicotine/BA-50 | 160    | 24       | 2200           | 4300           | 1.9 | 98        |
| 14  | nicotine/BA-50 | 160    | 36       | 5500           | 11 400         | 2.1 | 99        |
| 15  | nicotine/BA-50 | 160    | 48       | 5000           | 12 900         | 2.6 | 99        |
| 16  | nicorandil-50  | 160    | 36       | 4800           | 10 600         | 2.2 | 98        |

\*Determined from GPC. \*\*Determined from \(^1\)H NMR spectroscopy.
and confirms the occurrence of lactide molecules in the absence of any side reactions. Envelope B (x denotes even number of lactyl repeat units) and envelope C (x denotes odd number of lactyl repeat units) refer to BA-substituted PLLA chains which correspond to eq iv. The reason behind the occurrence of the odd and even envelopes of x is the backbiting of the propagating anionic species, which in turn results in the formation of macrocyclics, free of initiator eq v. Out of the four envelopes formed, the envelopes related to BA-terminated chains are found to be more prominent and hence BA can be regarded as the chain transfer agent.

Similarly, MALDI-TOF-MS spectra of PLLA conjugates synthesized by nicorandil shown in Figure 3 are found to be consistent with eq iv and hence confirm the growth of PLLA chains having nicorandil at its terminal end, occurring in the absence of any undesirable side reactions.

Hence, it can be clearly concluded that PLLA synthesized using nicotine and nicorandil grows in the absence of any unwanted side reaction. The reason behind this could be the association of the bulky group with the structure of the N-heterocyclic functionalized molecules which prevent substitution and in turn stop the backbiting reactions of the propagating anions. However, using BA as the coinitiator yields macrocyclic compounds because of the cyclization reaction.

NMR Analysis. Identification of the reactive species taking part during the ROP of LLA initiated using nicotine was carried out by recording 13C NMR spectra of PLLA conjugate samples. Figure 4 shows the 13C NMR spectrum obtained for PLLA using nicotine as the initiator, which exhibits strong signals because of methyl carbon, methyne carbon, and carbonyl carbon located at 16.7, 69.1, and 169.7 ppm, respectively, attributed mainly to PLLA chains. The nicotine carbons exhibit
weak signals and appear at 148.8, 138.8, 134.7, 123.5, 68.8, 56.9, and 39.9 as indicated by letters d, e, f, g, h, i, and j, respectively. An upfield magnetic shift in the Cα−N peak of nicotine has been observed at 148.8 ppm wrt the carbon atom.

Figure 5 shows the 13C NMR spectrum of PLLA synthesized via the polymerization of LLA using nicotine along with BA. Strong signals appear at 16.7, 69.1, and 169.7 ppm which are assigned to methyl carbon, methyne carbon, and carbonyl carbon, respectively, of the PLLA chains along with additional peaks which correspond to carbons associated with the benzyl ring at around 128.5, 128.6, and 128.7 ppm. Also, a peak at 67.0 ppm is observed which is attributed to −CH2 of BA attached to the PLLA chain. This clearly proves that BA partly substitutes nicotine on the PLLA chain. This observation also agrees with the spectrum (Figure 2) obtained from MALDI-TOF-MS analysis.

FTIR Analysis. Comparative FTIR spectra have been obtained for PLLA conjugates synthesized via the ROP of LLA by nicotine with and without BA as shown in Figure 6. Both spectra clearly show PLLA’s characteristic stretching frequencies for νas(CH3), νs(CH3), ν(COC), and ν(C−COO) at 2997, 2948, 1276, and 865 cm−1, respectively. A strong band present at 1757 cm−1 is attributed to the carbonyl group present in the PLLA chain. Bending frequencies for δas(CH3), δs(CH3), and δ(C–O) have been observed at 1458, 1386, and 756 cm−1, respectively. A sharp peak present at 1636 cm−1 corresponds to ν(C−N) which highlights the presence of the amide group. The C–O stretching frequencies of PLLA are observed at 1185 and 1086 cm−1.

Additionally, in both spectra, a broad peak is observed in the range of 3400–3500 cm−1 which is attributed to the stretching vibration of O–H in the hydroxyl group. A band appearing around 500–516 cm−1 corresponds to the in-plane bending of the O==C−N group formed by the nicotine fragment, which occurs at the terminal end of the PLLA chain. Thus, this is in good agreement with the MALDI-TOF-MS spectra, satisfying eqs i and ii. Furthermore, in combination with the above peaks, Figure 6b shows a peak at 701 cm−1 (ring C==C), which indicates the presence of BA-terminated PLLA chains and is in agreement with eqs iv−vi of MALDI-TOF-MS spectra.

Similarly, FTIR spectra of PLLA conjugates synthesized using nicorandil alone (Figure 7) consist of PLLA’s characteristic stretching frequencies for νas(CH3), νs(CH3), ν(C==O), ν(COC), and ν(C−COO) at 2998, 2946, 1756, 1277, and 865 cm−1, respectively. The absorption bands present at 1459, 1387, and 757 cm−1 correspond to bending frequencies for δas(CH3), δs(CH3), and δ(C==O), respectively. A sharp peak present at 1623 cm−1 corresponds to N–H amide bending of nicorandil. The C–O stretching frequencies of PLLA are observed at 1185 and 1087 cm−1. The band appearing around 515 cm−1 represents the in-plane bend of O==C−N of the nicorandil fragment, confirming the presence of nicorandil in the PLLA chain. This result is also well-explained by the MALDI-TOF-MS spectra (Figure 3). Also, a wide peak is present at 3501 cm−1 which occurs because of the hydroxyl group attached to the terminal end of PLLA.
Reaction Mechanism. We propose a generalized reaction pathway for N-heterocyclic functionalized molecules nicotine and nicorandil as initiators for polymerization carried out via the ROP of LLA as depicted in Scheme 1. First, LLA is initiated by the lone pair electrons of the N-heterocyclic nitrogen atom of the N-heterocyclic functionalized molecule forming an active anionic adduct (1a). Entity 1(a) sequentially adds up the molecules of LLA forming a PLLA chain having the N-heterocyclic functionalized molecule at its terminal end (1b), as confirmed by two equations (eqs i and ii) and eq vi as obtained in MALDI-TOF-MS analysis (Figures 1 and 3). Here, the ROP of LLA proceeds in the absence of side reactions, which may be because of the presence of steric hindrance in the initiator as suggested in an earlier work reported in literature.38

However, if LLA polymerization is carried out using BA, acting as the coinitiator, the benzyl oxide anion of BA takes part in transfer reactions with some of the growing chains of PLLA (1b) and follows path 1 (Scheme 1), generating a benzyl oxide-
terminated entity (1c), with the release of the N-heterocyclic functionalized molecule used. The released N-heterocyclic molecule can then be further utilized by the LLA left as the residue. Hence, under otherwise identical conditions, comparatively higher conversions are achieved in the case of polymerization carried out in the presence of a coinitiator, even though the molecular weight of PLLA obtained is found to be lower. Also, macrocycles (1d) are found to form when the coinitiator BA is used, as indicated by eq v in MALDI-TOF-MS spectra (Figure 2). This is one of the reasons for the yield of PLLA having a lower molecular weight when the polymerization of LLA was carried out in the presence of BA as compared to PLLA synthesized via the polymerization of LLA, initiated with the N-heterocyclic functionalized molecules alone.

Thus, Scheme 1 clearly shows that synthesis of PLLA conjugates via the ROP of LLA using N-heterocyclic functionalized molecules such as nicotine and nicorandil follows an anionic chain growth mechanism in the presence of side reactions such as transesterification reactions. However, side reactions occur only when the polymerization is carried out in the presence of a small amount of a coinitiator such as BA or when there is no steric hindrance in the initiator.

**Effect of Reaction Parameters on the ROP of LLA Using Nicotine as the Initiator. Effect of Reaction Time and Temperature.** A set of ROP reactions using nicotine as the initiator have been performed. GPC studies revealed that number average molecular weight, $M_n$, is found to increase with time and reaches its highest value at 36 h for the reactions carried out at 160 °C as shown in Figure 8. The $M_n$ as well as percentage conversion increase up to 36th h of polymerization, beyond which a decreasing trend is observed for the same.

![Figure 8](image)

Figure 8. Plot of $M_n$ as a function of nicotine-initiated reaction time for [L]/[I] = 50.

Also, to determine the effect of ROP temperature, experiments have been performed varying the temperature, and the highest $M_n$ value has been observed for the reactions carried out at 160 °C, as shown in Figure 9. Subsequently, it has been observed that for reactions conducted at a high temperature, that is, 180 °C, there is a gradual reduction in $M_n$ as well as percentage conversion (Table 1). Herein, at 160 °C, molecular weight is found to increase during the whole polymerization course, and only the propagating entity 1b is observed in MALDI-TOF-MS spectra (Figure 1). However, ROP carried out at 160 °C using nicotine + BA for 36 hours yields comparatively low $M_w$ PLA because of the yield of isolated entities 1c and 1d. Undesirable side reactions such as transesterification or termination reactions may occur at higher temperatures mainly via the terminal anionic end groups. These anionic species dominate over propagating chains and thus, the polymerization proceeds more rapidly with temperature, which in turn also affects the rates of side reactions such as transesterification, backbiting, and chain redistribution. Thus, to achieve the desired high $M_n$ PLLA, polymerization should be preferably performed at a temperature of 160 °C for 36 h in the absence of BA.

**Effect of Nicotine Concentration as the Initiator.** The effect of the nicotine concentration as the initiator on the polymerization of LLA was determined by varying the molar ratio of LLA to nicotine, [L]/[I] = 50–500 at the optimum ROP temperature and time, that is, at 160 °C for 36 h. The results concluded that both $M_n$ as well as monomer conversion of PLLA decrease as the [L]/[I] molar ratio increases from 50 to 500, as shown in Figure 10. Similar published work on the ROP of LLA using N-heterocyclic molecules such as PDP,
imidazole, and so forth also showed a similar pattern in the $M_n$ of PLLA wrt the initiator concentration. Herein, at the LLA to nicotine molar ratio ([L]/[I]) = 50, the nicotine concentration is maximum, providing the highest value of $M_n$, and the $M_w$ value gradually decreases as the concentration of nicotine decreases.

**Kinetics Study of the Nicotine-Initiated ROP of LLA.** The kinetics parameters during polymerization were investigated to examine the rate of the nicotine-initiated ROP of LLA. $^1$H NMR has been recorded to determine the conversion for the kinetics studies. A plot of the residual monomer as a function of the reaction time is depicted in Figure 11 which reveals an exponential-like decay in the temperature range of 120−160 °C, indicating that the nicotine-initiated ROP of LLA satisfies first-order kinetics in terms of the monomer concentration. The data produced yield a good fit to the assumption of the apparent rate constant, $k_{app}$, which increases with the increase in the ROP temperature from 120−160 °C.

Accordingly, the activation energy, $E_a$, of ROP is determined experimentally using the Arrhenius equation, $k_{app} = A e^{(-E_a/RT)}$ with $k_{app}$ values (0.0019, 0.0027, and 0.0031 min$^{-1}$) obtained from Figure 11 at 120, 140, and 160 °C yielding a low activation energy value of 4.9 kcal·mol$^{-1}$ which is found to be lower than that reported for the PDP-initiated anionic ROP of LLA (5.6 kcal·mol$^{-1}$)$^{43}$ and the coordination insertion mechanism of LLA (19.55 kcal·mol$^{-1}$)$^{28,39}$.

**Effect of the Nicotine Concentration on the Reaction Rate.** The functional form of the polymerization rate describing this system can be considered as $-d[L]/dt = k_{app}[L]$, where $k_{app}$ represents the apparent rate constant and is related to the initiator concentration as $k_{app} = k_{abs}([L]/[I])^a$, where $k_{abs}$ represents the absolute reaction rate constant. A plot of $k_{app}$ values (obtained from Figure 12) versus initial initiator concentration $[I_0]$ is plotted, and the slope of the curve gives the value of exponent “a” as −0.8. Thus, it can be inferred that nicotine-initiated ROP satisfies first-order reaction kinetics in terms of the initiator concentration.

**Hyphenated TG–FTIR Analysis of Evolved Gases.** The thermal stability of the synthesized PLLA samples has been analyzed using the thermogravimetric analysis (TGA) technique. TGA has been coupled with FTIR to obtain detailed information about the evolution of volatile components at various stages during the thermal degradation process. The trends of the thermogram (TG) and differential TG curves of PLLA conjugates are shown in Figure 13a,b. As it can be seen from the graph, temperature $T_{10}$, at which 10% weight loss occurs, is found to be 298 °C, and the maximum degradation temperature ($T_{max}$) is found to be at 381 °C. Similarly, the TG curve (Figure 13b) of PLLA synthesized using nicorandil clearly depicts $T_{10}$ at 292 °C and $T_{max}$ at 378 °C. In the GS (Gram-Schmidt Curve), only one peak is noticeable in both curves which indicate that degradation occurs in a single step and the volatile products are detectable beyond 277 °C.
Figure 14. Temperature-based 3D FTIR spectra of the thermal degradation of PLLA synthesized via the ROP of LLA using nicotine in an argon atmosphere (a); stack plots for characteristics spectra of the degradation products recorded at various temperatures (b).

Figure 14a,b displays the 3D FTIR spectrum and stack plots, respectively, corresponding to the thermal degradation of PLLA synthesized using nicotine by heating at the rate of 10 °C/min under an argon atmosphere in a continuous mode. Figures 14b and 15b illustrates the stacked IR spectra for the main decomposition process of PLLA synthesized using nicotine and nicorandil from intervals 277−420 °C and 274−418 °C, respectively. As reported in literature,45,46 the main decomposition product, lactide, shows characteristic bands because of \( \nu (C-H) \), \( \nu_{as}(CH_3) \), and \( \nu_{s}(CH_3) \) at 3006, 2958, and 2893 cm\(^{-1}\). The high intensity of the band at 1792 cm\(^{-1}\) (\( \nu(C=O) \)), 1238 and 1110 cm\(^{-1}\) (\( \nu(C=O-C) \)), and 933 cm\(^{-1}\) (ring skeleton), and carbon dioxide (\( \nu_v(2358−2340) \) cm\(^{-1}\)) are also detectable above the onset temperature in both cases. It can thus be inferred that the major volatile products of thermal decomposition of PLLA are released with the highest intensity at the \( T_{max} \). It is also noticed that the intensity of absorption bands corresponding to different volatile products increases gradually with the increase of temperature. This is in agreement with the TGA plots, and the intensity of absorption band continuously decreases after the highest peak. Moreover, the absorption related to carbon dioxide at bands 2358−2310 cm\(^{-1}\) (\( \nu_v(O=O) \)) and 669 cm\(^{-1}\) (\( \delta(O=O) \)) and double apex related to carbon monoxide at 2176−2118 cm\(^{-1}\) (\( \delta(C=O) \)) also appeared till the end of the thermal decomposition but with a lowered intensity.

Figure 16 depicts the comparison between the FTIR spectra of PLLA synthesized using nicotine and nicorandil. The slight differences are in the wave number ranges of 2600−3000 cm\(^{-1}\) and 1000−1500 cm\(^{-1}\). From the FTIR profiles, it can be interpreted that the total amount of volatile products for PLLA synthesized using nicorandil is lower than that from nicotine. Almost no water is evolved in the case of PLLA synthesized using nicorandil, although there is an evolution of water in the case of nicotine. A small amount of CO\(_2\) is observed in the thermal decomposition of PLLA synthesized using nicorandil which might be because of the lowest intensity of the carbonyl group (C═O).

For PLLA synthesized using nicotine inspecting the IR spectra at \( T_{max} \) the peaks at 1117−1189 cm\(^{-1}\) (CH\(_2\) wag),
1418–1478 cm\(^{-1}\) (in-plane and sym C–H wag), and 717 cm\(^{-1}\) (out-of-plane δ(C–H)) can be associated with pyridine.\(^{47}\) In addition, there are coinciding absorption peaks of 2779 cm\(^{-1}\) (N–CH\(_3\)) present in nicotine and 2738 cm\(^{-1}\) (C–H stretching, ν\(_s\)(CHO)) in aldehyde which is evolved from degradation of PLLA. This indicates that the generation of aldehyde and the release of nicotine occur at the same time. It demonstrates that the release of nicotine is confirmed at the mass loss stage (381–395 °C) with the absorption bands disappearing above 395 °C in the IR spectra. Thus, nicotine is released from the synthesized PLLA–nicotine conjugates along with reduced toxins upon its exposure to heat, which opens up a new area of its high-end applications in developing toxin-free synthetic cigarettes and in the biomedical field. The new advent peaks at 2930 and 2821 cm\(^{-1}\) belong to ν\(_s\)(CH\(_2\)) and ν\(_{as}\)(CH\(_2\)), respectively, and this indicates the formation of alkane and alkyl substitutes.\(^{48}\) In addition, the peak at 1033 cm\(^{-1}\) is attributed to ν(C–O) for methanol in the FTIR spectra.\(^{49,50}\) Lactide is identified by the bands at 3006 cm\(^{-1}\) (ν(C–H)), 2952 cm\(^{-1}\) (ν\(_{as}\)(CH\(_3\))), 2893 cm\(^{-1}\) (ν\(_s\)(CH\(_3\))), 1792 cm\(^{-1}\) (ν(C=O)), 1452–1381 cm\(^{-1}\) (δ(CH\(_3\))), 1242 and 1106 cm\(^{-1}\) (ν(C=O–C)), and 930 cm\(^{-1}\) (ring skeleton). Two prominent absorption bands at 1762 cm\(^{-1}\) (ν(C=O)) and 2738 cm\(^{-1}\) (C–H stretching, ν(CHO)), weak bands at 2963 cm\(^{-1}\) (ν\(_a\)(CH\(_3\))) and 1371 cm\(^{-1}\) (δ(CH\(_3\))) described that aldehyde is also formed during the degradation of PLLA. The FTIR spectrum of the evolved gases shows the production of water from the peaks 3638 cm\(^{-1}\) (ν\(_a\)(OH)) and 3577 cm\(^{-1}\)
(ν₃(OH)) generated by the cleavage of hydroxyl groups. Formation of the NO₃⁻ compound is confirmed because of the signal observed at 1352 cm⁻¹ in PLLA synthesized using nicorandil which is overlapped with many small peaks at this region.

## CONCLUSIONS

This work reports the successful synthesis of metal-free PLLA conjugates via the ROP of LLA using nicotine as well as nicorandil drug molecules as initiators via the N-functionalized initiation of these molecules without any side reactions. MALDI-TOF-MS analysis confirmed the existence of the initiator at the terminal end of the PLLA chain. On the basis of the analysis, an anionic mechanism has been proposed for the ROP of LLA carried out using nicotine in the presence and absence of a coinitiator. Also, kinetics studies have revealed that the nicotine-initiated ROP of LLA satisfies first-order kinetics in terms of LLA and initiator concentration with an activation energy which is found to be lower than that for PDP-initiated ROP as well as tin octoate-initiated ROP. These N-heterocyclic functionalized molecules, thus, are proved to be acting as initiators for synthesis of PLLA. Further, thermal release studies performed by TG–FTIR analysis found that nicotine is released from these synthesized PLLA–nicotine conjugates. Thus, these PLLA–nicotine conjugates may effectively be used in tobacco industries to prepare synthetic cigarettes because of their characteristic release of nicotine with reduced toxins upon their exposure under heat and may also be useful for biomedical applications such as drug delivery.

## EXPERIMENTAL SECTION

**Materials.** PLLA has been synthesized in the laboratory from L-lactic acid, ≥99%, PF 90, Purac (The Netherlands) and recrystallized two times using distilled ethyl acetate and kept under vacuum drying for 24 h prior to use. N-heterocyclic functionalized molecules such as nicotine (≥99%, GC grade) in the liquid form and nicorandil (≥98%, HPLC grade) in the powder form were obtained directly from Sigma-Aldrich (India) and explored as initiators for the synthesis of PLLA conjugates. Chloroform, BA, and acetone were purchased directly from Merck-India.

**ROP Procedure.** Initially, PLLA has been recrystallized two times using distilled ethyl acetate and dried under vacuum for 24 h prior to use. ROP reactions have been performed in glass ampoules sealed under vacuum. The glass ampoules were first filled with the monomer (LLA), and then the calculated amount of the initiator, with varying LLA to the initiator molar ratio ([(L)/[I]]) in the range of 50–500, is subsequently added to the ampoules. Fewer polymerization reactions have been carried out using a coinitiator such as BA, where the composition of the initiator: coinitiator is kept equimolar.

Then, the ampoules were vacuum-dried while being immersed in an oil bath maintained at a temperature of 60 °C for a period of 2 h. After two hours, the ampoules were sealed under vacuum and kept for polymerization within the temperature range of 120–180 °C in a hot air oven attached with an inbuilt magnetic stirrer. At the predetermined reaction time interval (12, 24, 36 and 48 h), the glass ampoules were removed, and the polymer was cooled by dipping the ampoule in ice-cooled water to stop polymerization. Finally, the sealed ampoules were broken and the contents analyzed for characterizations.

**Characterizations.** Gel Permeation Chromatography. Number average [Mₙ] and weight average [Mₘ] molecular weights have been obtained using Shimadzu’s Prominence GPC (Prominence GPC RID-10A detector) with two PL gel 5 μm (300 × 7.5 mm) columns used for separation, calibrated with polystyrene standards in chloroform.

Fourier Transform Infrared Spectroscopy. FTIR spectra of PLLA samples were recorded with a PerkinElmer Frontier FTIR spectrometer; samples were grounded into a powdered form and were evaluated using the KBr pellet technique in transmission in the spectral range of wavenumber 4000–450 cm⁻¹ having a resolution of 4 cm⁻¹ at an average of 16 scans. Synthesized PLA is dissolved in chloroform and subsequently precipitated in methanol to remove unreacted lactide and nicotine from the product.

MALDI-TOF-MS. MALDI-TOF-MS analyses have been performed using a Bruker Autoflex Speed MALDI-TOF mass spectrometer, employing a 19 kV accelerating voltage with each spectrum scanning 500 shots. The sample preparation is done using an α-cyano-4-hydroxy-cinnamic acid matrix (10 mg mL⁻¹). The analyte solution (1 μL, 10 mg mL⁻¹) is first mixed with 1 μL of matrix solution (50:50 v/v, CHCA/acetonitrile) and then put onto a stainless steel sample plate and allowed to dry.

Nuclear Magnetic Resonance Spectroscopy. To identify the species taking part during the ROP of LLA, the synthesized PLLA samples are analyzed via ¹H and ¹³C NMR measurements in deuterated chloroform (CDCl₃) at ambient temperature on a Bruker 600 MHz NMR spectrometer. ¹H NMR analysis has been done to study the conversion for kinetic studies. The residual LLA at various ROP conditions has been determined using eq (vi).

Percent of the remaining monomer (W/W %) is calculated using equation

\[
(W/W) = \frac{I_{q,\text{LLA}}}{I_{q,\text{LLA}} + I_{q,\text{PLLA}}} \tag{vii}
\]

where, \(I_{q,\text{LLA}}\) and \(I_{q,\text{PLLA}}\) are the integral areas of peaks related to the lactide (LLA) and polymer methine quartets (PLLA) located at 5.04 and 5.2 ppm, respectively. Low reaction time has been chosen to find out the noticeable change in the conversion which is low at initial polymerization.
The kinetics parameters are investigated to examine the rate of nicotine-initiated the ROP of PLLA. Experiments have been performed at different temperatures (120, 140, and 160 °C) for 30, 60, 90, 120, and 150 min by keeping the L/I ratio (50) constant. The obtained products from the reaction are analyzed, and conversion for kinetics studies is determined via $^1$H NMR.

**Thermogravimetric Analysis.** Thermal stability has been determined using a PerkinElmer TGA 4000 thermogravimetric analyzer at a heating rate of 10 °C min$^{-1}$ in the temperature range of 30–600 °C under argon flow. TGA analyzer is coupled to FTIR (Frontier 4000) through a TL 8000 transfer line. High purity argon gas with a flow rate of 50 mL min$^{-1}$ is applied to maintain the inert atmosphere. The FTIR spectra are recorded in the spectral range of 4000–450, and 8 cm$^{-1}$ resolution is selected at an average of 4 scans.

### AUTHOR INFORMATION

**Corresponding Author**

*E-mail: vkatiyar@iitg.ernet.in, vimal.katiyar@gmail.com*  
(V.K.)

**ORCID**

Vimal Katiyar: 0000-0003-4750-7653

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