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SYNTHESIS AND CHARACTERIZATION OF AMPHIPHILIC POLY ETHYLCYANOACRYLATE FOR DRUG DELIVERY

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ABSTRACT

Alkyl cyanoacrylates are found to be promising compound for utilizing both as medical adhesive & drug delivering agent for various molecules such as proteins, anti-neo plasting agent, anti-microbial agent & so on. As according to reported procedure alkyl cyanoacrylates were synthesized by utilizing LR grade reagents & under inert condition. The compound was synthesized as according to reported procedure & progress of reaction was determined by the help of TLC. Synthesized compound shows the characteristic properties & it was found to be as similar according to reported procedure such as its solubility in acetone. The structural conformation was done by performing FTIR & 1 H NMR Spectroscopy. Absence of C=C bond (stretching vibration) at 1616cm^{-1} (which was only seen in monomer) indicates the polymerization because this C=C bond only appear in the monomer. The -CN peak shifts from 2239.4 to 2248.8 cm^{-1} & it's a diminished peak indicates polymerization of compound. Synthesized compound shows the absence of singlets which were seen only into the monomer at δ 6.5 ppm & δ 7.5 ppm. At δ 4.3 ppm & δ 1.3 ppm peaks generated due to protonpresent in ethyl side chain CH3 & CH2. At δ 2.6 ppm & δ 3.0 ppm peaks were arised due to proton of CH2. The peak atδ1.9ppm & δ1.0 ppm were due to –CH3 & =CH2 of ethanol & these were present both into monomer & polymer. Only oligomer of ethyl cyanoacrylate was synthesized because during thermal depolymerization of ethyl cyanoacrylate oligomer charring was observed which was supposed due to high temperature & vacuum.

INTRODUCTION

It involves the transportation of drug or active pharmaceutical ingredient or it's formulation from the site of administration to the site of action, for obtaining desired therapeutic effect with minimal side effects. Drug delivery is concerned with both quantity and duration of the presence of API or Drug. Drug delivery technologies modify the drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Drug delivery is basically influence by dosage form & route of administration in such a way that active drug is available at site of action for specific duration.

Biodegradation of PACA ester

In general PACA ester degrades both in buffers at neutral pH, in cell medium with serum & in human serum. Biodegradation of PACA ester is due to presence of esterase enzyme. If PACA ester is administered such that surrounding medium consist of hydrolytic enzyme, then, hydrolysis of PACA ester occurred which was responsible for production of alkyl alcohol and cyanoacrylic acid. This product was water soluble & eliminated through kidney. Alternatively, PACA esters undergo reverse knoevengeal reaction responsible for producing cyanoacetic ester & formaldehyde. This is due to presence of water responsible for biodegradation of PACA ester.

Mechanism of drug release from PACAs

Depending upon the type of drug loading different mechanism of drug release are noticed. Drug which are absorbed on surface of pre-synthesized Nano -particles are released by desorption. Entrapped drug which are weakly bound to polymer are released by diffusion. Drugs which have high affinity to polymer are released very slowly by diffusion & can be released during bio erosion of polymer. In such condition release of drug takes place via complete bio erosion of polymer which was carried out by hydrolyzing the ester bond.

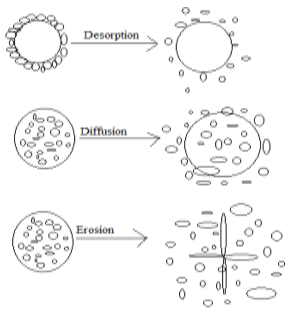


Fig. Mechanism of drug release from PACA polymer.

Recently utilized cyanoacrylate polymers

For drug delivery purpose, amphiphilic cyanoacrylate polymers were utilized. The use of hydrophilic polymer or moiety such as hyaluronic acid or PEG was utilized both as surface modifying agent & making cyanoacrylate as an amphiphilic polymer. Amphiphilic cyanoacrylate polymers were prepared by dissolving cyanoacrylate monomer into suitable polymerizing medium at acidic pH consisting of hydrophilic moiety with good stirring for a suitable time followed by isolation & drying of amphiphilic cyanoacrylate polymer. Such types of polymers were used as drug delivery agent for certain diseases such as cancer, in gene therapy etc.

MATERIAL AND METHOD

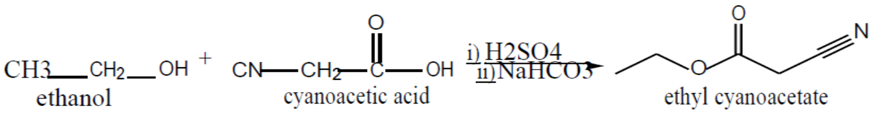
MATERIAL

S.No	Chemical Name	Batch No	Manufacturer	CAS No
1	Ethanol	R0381319	Rankem	67-56-1
2	Cyanoacetic acid	L178831603	Loba chemie pvt.ltd	372-09-8
3	Ethyl acetate	R101F04	Rankem	141-78-6
4	Hexane	LH253007	Loba chemie pvt.ltd	110-54-3
5	Silica gel G	#L136511503	Rankem	112926-00-8
6	Paraformaldehyde	CF130509	Qualikemes	30525-89-4
7	Glacial acetic acid	37013l05	SDFCL	64-19-7
8	Piperidine	#LM02771504	Loba chemie pvt.ltd	110-89-4
9	Phosphoric acid	#L116841401	Loba chemie pvt.ltd	7664-38-2
10	Hydroquinone	G008J17	Rankem	123-31-9
11	Phosphorus pentoxide	J031A08	Rankem	1314-56-3
12	Poly ethylene glycol 300	#L121941410	Loba chemie pvt.ltd	25322-68-3
13	Suphuric Acid	UN1789	Loba chemie pvt.ltd	7647-01-0
14	Sodium bicarbonate	#SL334J1202	Loba chemie pvt.ltd	497-19-8
15	Ethyl cyanoacetate	LH174431510	SDFCL	1043-52-4

METHOD

Procedure for the Synthesis of ethyl cyanoacetate

In clean & dry 100ml RBF, 10ml (0.35mmoles) of absolute ethanol was taken. Then, accurately weighed 18gm (0.2mmoles) of cyanoacetic acid was added to it followed by addition of single drop of concentrated sulphuric acid. Afterwards, this reaction mixture was heated over oil bath under reflux for 3hrs. at 60°. Excess of alcohol & formed water was then removed under reduced pressure. After removal of alcohol & water, again 10ml (0.35mmol) of absolute & single drop of concentrated sulphuric acid was added. Reaction mixture was again heated for 2hrs at 60°C over oil bath under reflux. Excess of alcohol& formed water was then removed under reduced pressure. Ester was then allowed to cool at room temperature; sulphuric acid was then neutralized by the help of saturated solution of sodium bicarbonate, ester upper layer was then collected & stored.



Reaction scheme2: Synthesis of ethyl cyanoacetate.

Determination of Rf value

Rf value of synthesized Compound was determined by thin layer chromatography (TLC) prepared over glass slides using Silica Gel G. The solvent system used was Hexane: Ethyl acetate (5:5) for both butyl cyanoacetate & ethyl cyanoacetate. The TLC plates were activated for 60 min at 110°C. The spots were applied on silica gel plate and the plate was run in a saturated solvent system chamber. The spots on the plate were detected by the help of Iodine vapor. Rf values are reported.

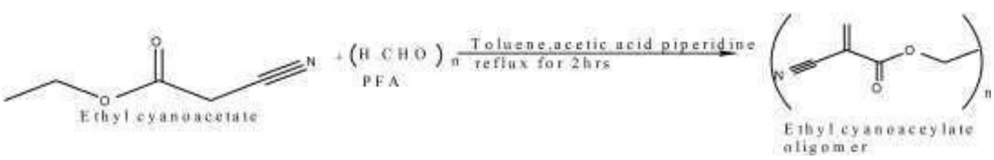
$$Rf\ Value = \frac{Distance\ travelled\ by\ solute}{Distance\ travelled\ by\ mobile\ phase}$$

Table: Rf Value determination.

S.NO	Compound	Solvent System Used	Rf
1.	Ethyl cyanoacetate	Hexane: Ethyl acetate (5:5)	0.45

PROCEDURE FOR SYNTHESIS OF ETHYL CYANOACRYLATE OLIGOMER

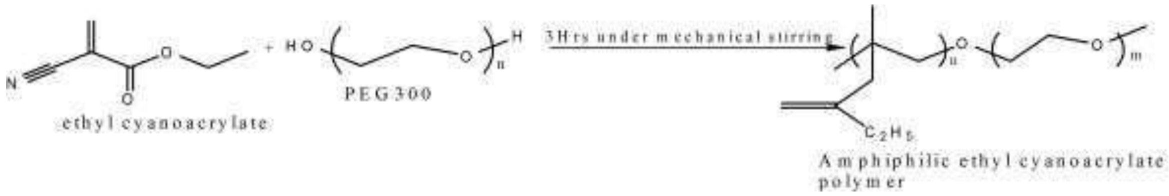
Ethyl cyanoacetate was synthesized by following the reflux procedure. It gives low yield product therefore; ready-made marketed ethyl cyanoacetate was utilized for further procedure. Clean & dry quick fit 100 ml RBF was taken, accurately weighed amount of 10mmol (1.067 ml) of ethyl cyanoacetate was taken & 1ml of toluene was then added. Afterwards, 10mmol(0.30025gm) of paraformaldehyde was added followed by addition of one drop of acetic acid & one drop of piperidine. At 90°C for 2hrs reaction mixture was heated under reflux condition, followed by the azeotropic distillation of water, remaining water was then removed under reduced pressure. Neutralization of base was done by addition of one drop of phosphoric acid; ethyl cyanoacrylate oligomer was then obtained.



Reaction Scheme 3: Synthesis of ethyl cyanoacrylate oligomer.

Procedure for synthesis of amphiphilic ethyl cyanoacrylate polymer

Obtained ethyl cyanoacrylate oligomer was then subjected to thermal depolymerization in the presence of hydroquinone 150mg (14.846mmol) & phosphorus pentoxide 400mg (39.591mmol). Under vacuum & in steam of sulphur dioxide gas at 180°C reaction proceeded & crude monomer (ethyl cyanoacrylate) was obtained in presence of small amount of hydroquinone & phosphoric anhydride. Under mechanical stirring, obtained crude monomer was then subjected to10ml of aqueous polymerizing medium which consist of 2% w/v PEG 300 at pH 2. It was then stirred for 3hrs, results in formation of milky white amphiphilic ethyl cyanoacrylate polymer.



Reaction scheme 4: Synthesis of amphiphilic ethyl cyanoacrylate polymer.

Spectral analysis of synthesized compounds

Infra-red spectroscopy

FTIR spectra of the synthesized compound was carried out at SICART Mota Bazaar, Vallabh Vidyanagar, Anand, Gujarat, on Perkin Elmer Spectrum FTIR spectrophotometer by using KBr pellet method. The IR frequencies of the compound were reported.

Nuclear Magnetic Resonance Spectroscopy (IHNMR)

NMR spectra of the synthesized compound was recorded in SICART Mota Bazaar, Vallabh Vidyanagar, Anand, at 400 MHz using BrukeAdvance III 400 NMR spectrometer instrument and by using deuterated acetone as a solvent.

RESULT AND DISCUSSION

All reagents used for synthesis were of synthetic grade. Structures of all the compounds were confirmed by using IR & NMR Spectroscopy.

Interpretation of FTIR Spectra

The FTIR Spectra of synthesized compound was recorded between the wave region of 500-1400cm^{-1} by using Perkin Elmer Spectrum FTIR spectrophotometer. Structure confirmation of sample was done by interpretations of characteristic absorption stretching & bending band of spectral graph.

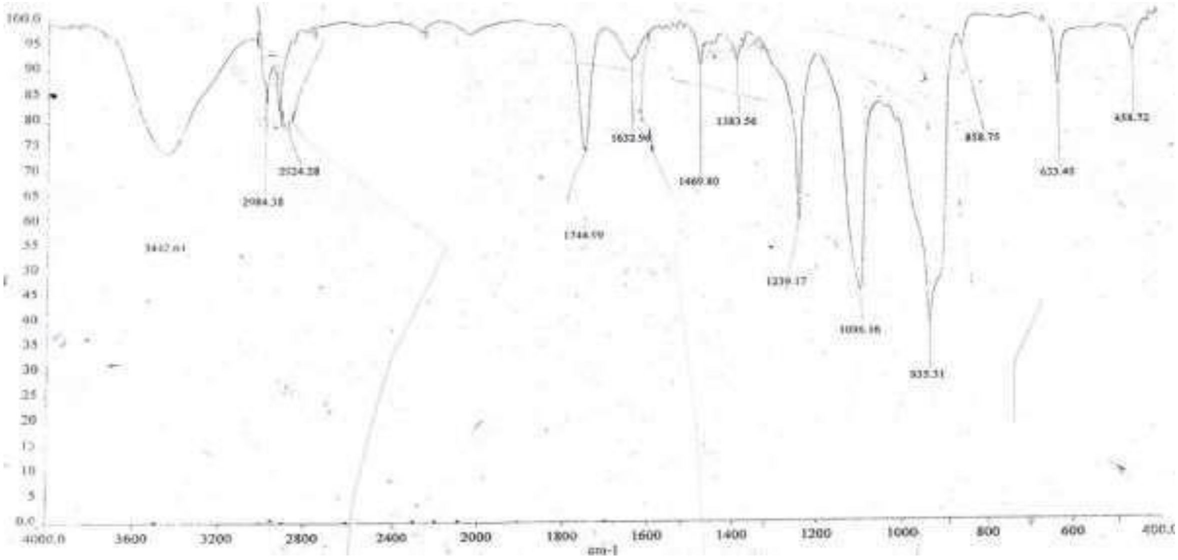


Fig: IR Spectrum of synthesized compound.

FT-IR Result

The synthesized compound shows the absence of C=C bond (stretching vibration) at 1616cm^{-1} (which was only seen in monomer) indicates the polymerization because this C=C bond appear only in the monomer. At 3131.cm^{-1} synthesized compound shows the absence of stretching vibration which was due to vinyl structure of (=CH_2, =CH-) which was only observed into monomer but not in polymer. The peaks at around 3080–2800 cm^{-1} are arised due to CH_3 & CH_2 group of alkyl side chain of ester which remain same in both polymerized & unpolymerized condition. The -CN peak shifts from 2239.4 to 2248.8 cm^{-1} & it's a diminished peak indicates polymerization of compound. At 3442.64cm^{-1}shows the stretching vibration due to presence of secondary amine(catalyst). Stretching Vibration at 1744.99 cm^{-1} was observed due to C=O of aromatic amide(formed as impurity, by product during reaction). At 1469.80 C=C stretching vibration was observed indicates the formation of aromatic amide. At 1632.96 stretching vibration due to N-H was observed because of the aromatic amide.

Interpretation of NMR Spectra

NMR spectra of the synthesized compounds was recorded on 400MHz using Bruker Advance III NMR spectrometer instrument and by using deuterated acetone as a solvent. Structure confirmation of sample was done by doing interpretations of chemical shifts values of proton present in compound.

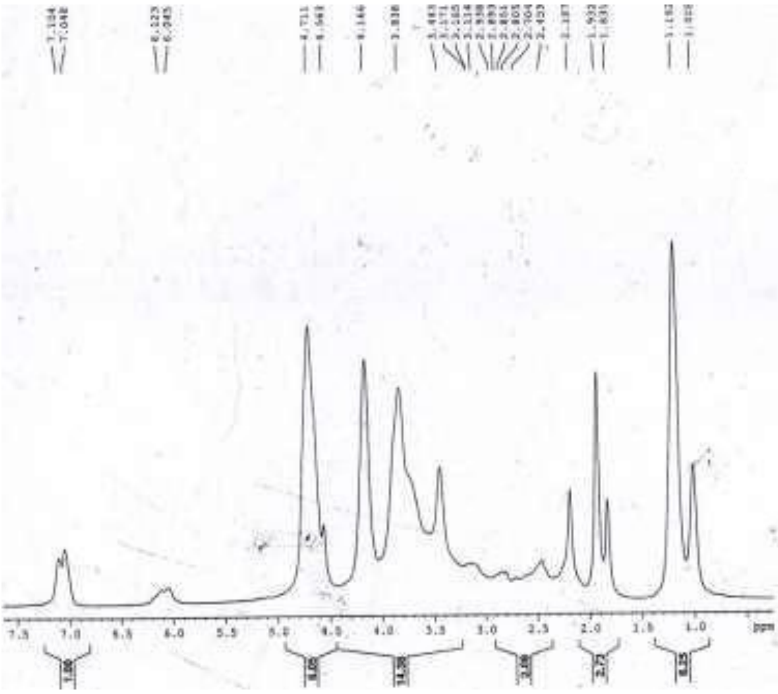


Fig: NMR Spectra of synthesized compound.

NMR RESULT

Synthesized compound shows the absence of singlets which were seen only into the monomer at δ 6.5 ppm & δ 7.5 ppm. At δ 4.3 ppm & δ 1.3 ppm peaks generated due to proton present in ethyl side chain CH_3 & CH_2. At δ 2.6 ppm & δ 3.0 ppm peaks were arised due to proton of CH_2. A pair of two doublet in the region between δ 6.0-δ 7.0 ppm arises due to solvent used and formation of aromatic amide as impurity (by product). At δ 4.56 – δ 4.71 ppm peaks were generated due to proton of unsaturated aromatic ring. At δ 3.17 – δ 3.14 ppm peak arise due to proton of nitrogen which was attached to carbonyl of aromatic ring. At δ 3.5 ppm peak arise due to proton of $=CH_2$ at adjacent to at electron withdrawing group (-CN. The region between δ3.0 - δ3.2 ppm peaks were generated due to ethanol. This is so because due to hydrolysis of ester (ethyl cyanoacetate in neglible con.) in the presence of catalyst and also due to reaction condition. At δ2.4 ppm the peak generated due to proton of nitrogen of catalyst. At δ 2.2 ppm the peak was arises due to proton of $–CH_3$ attached to aromatic ring. The peak at δ2.0 ppm was arised due to presence of unreacted ester. The peak at δ1.9ppm & δ1.0 ppm were due to $–CH_3$ & $=CH_2$ of ethanol.

Amphiphilic polymer of ethyl cyanoacrylate was not synthesized because during thermal depolymerization of ethyl cyanoacrylate oligomer charring was occurred. This was may be due to high temperature & applied vacuum.

SUMMARY AND CONCLUSION

In the synthesis of cyanoacrylates, reaction between alkyl cyanoacetate & paraformaldehyde was carried out in the presence of mild base with azeotropic distillation of water which was formed during reaction followed by neutralization of base & thermal depolymerization of low molecular weight poly alkyl cyanoacrylate in the presence of acidic medium & free radical stabilizers for obtaining crude alkyl cyanoacrylate monomer.

The major drawback of alkyl cyanoacrylate was because of the existence of two electron withdrawing functional group i.e; nitrile & ester group responsible for cyanoacrylates require certain stabilizers such as hydroquinone, for preserving cyanoacrylate at room temperature, until the time of utilization. In addition to this, it was found that cyanoacrylate along with its substituents shows histotoxicity to tissues, cyanoacrylate polymer itself often spontaneously degrades to formaldehyde and cyanoacetate compounds, which were accumulated within treated areas. This drawback was overcome by utilizing higher length of alkyl side chain into the cyanoacrylate ester.

The compound was synthesized as according to reported procedure & progress of reaction was determined by the help of TLC. Synthesized compound shows the characteristic properties & it was found to be as similar according to reported procedure such as its solubility in acetone.

The structural conformation was done by performing FTIR & 1 H NMR Spectroscopy. Absence of C=C bond (stretching vibration) at 1616cm^{-1} (which was only seen in monomer) indicates the polymerization because this C=C bond only appear in the monomer. The -CN peak shifts from 2239.4 to 2248.8 cm^{-1} & it's a diminished peak indicates polymerization of compound.

Synthesized compound shows the absence of singlets which were seen only into the monomer at δ 6.5 ppm & δ 7.5 ppm. At δ 4.3 ppm & δ 1.3 ppm peaks generated due to proton present in ethyl side chain CH_3 & CH_2. At δ 2.6 ppm & δ 3.0 ppm peaks were arised due to proton of CH_2. The peak atδ1.9ppm & δ1.0 ppm were due to –CH_3 & =CH_2 of ethanol & these were present both into monomer & polymer. Only oligomer of ethyl cyanoacrylate was synthesized because during thermal depolymerization of ethyl cyanoacrylate oligomer charring was observed which was supposed due to high temperature & vacuum.

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