Preparation of Poly (N-4-Antipyrinyl or Procainyl Methyl Nadamic Acids) as Drug Polymers

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Abstract

Two new monomers of N-4-antipyrinyl methyl nadamic acid M_1 and N-Procaienyl methyl nadamic acid M_2 were synthesized from reaction of 4-Aminoantipyrine or procaine with methyl nadic anhydride at room temperature with dioxane as a solvent.

The prepared monomers M_1 and M_2 were polymerized free radically with AIBN as initiator to corresponding polyamic acids P_1 and P_2, which were converted to their sodium salt polymers P_3 and P_4 to enhanced their solubility's in water.

The physical and chemical properties were studied for monomers and polymers, also FT-IR, 1H-NMR and UV. Spectroscopy was characterized of M1or M2. The intrinsic viscosity was measured by Ostwald viscometer at 30 ^{0}C .The swelling % was measured and the controlled release rates of drug polymers were studied in different pH values at 37 ^{0}C.

Keywords: Preparation; N-4-Antipyrinyl or procaine Amic Acids; Drug Polymers

Introduction

Antipyrine and its derivatives possess interesting pharmacological properties [1]. But, comparatively little is known about complexes of antipyrine derivatives with 3d-metal ions, especially their thermal studies .In view of this, and as part of interest on thermal aspects of antipyrine derivatives, it was a report regarding the thermal studies of a new series of cobalt (II) complexes of a Schiff base antipyrine

ligand containing a variety of counter ions such as, nitrate, chloride, bromide and iodide [2]. An interesting series of cobalt Π complexes of the new ligands 4-[(N-benzalidene) amino] antipyrine thiosemicarbayone was synthesized [3]. The enzymatic synthesis of N-protected L-amino acyl and L-peptidyl antipyrine amides was accomplished by proteases from different classes. Serrine and Cystine protease proved to be suitable tools for the production of amino acids and peptides conjugated to 4-aminoantipyrine [4].

Procaine is a local anesthetic drug of the amino ester group. It is used primarily to reduce the pain of intramuscular injection of penicillin, and it was also used in dentistry. Owing to the ubiquity of the trade name Novocain, in some regions procaine is referred to generically as novocaine. It acts mainly by being a sodium channel blocker [5].

Procaine was first synthesized in 1905 [6], shortly after amylocaine, and is the oldest man-made local anesthetic still in clinical use. It was created by the German chemist Alfred Einhorn who gave the chemical the trade name Novocaine, from the Latin nov- (meaning new) and -caine, a common ending for alkaloids used as anesthetics. It was introduced into medical use by surgeon Heinrich Braun.

Poly (N-procainyl amic acids) was prepared as drug polymer [7], Maleic and itaconic anhydride were polymerized free radically then allowed to react with different primary amines producing high yield of the polyamicacids [8-9].

The use of functional polymers in medicine has seen considerable growth during the past two decades [10]. Polymers as biomaterials have found applications in such areas as artificial organs, tissue engineering, components of medical devices, and dentistry. A growing aspect of the field is the recognition of polymers as useful therapeutic agents, ie, either polymers that exhibit pharmacological properties themselves, or that can be utilized as carriers for selective and sustained

delivery vehicles for small molecule or macromolecular (eg proteins, genetic materials, etc) pharmaceutical agents.

There has been a growing literature pertaining to the use of functional polymers as delivery agents for therapeutics against a variety of disease states. They include delivery of drugs at a sustained rate, targeted delivery of drugs at specific sites (to minimize toxicity and enhance selectivity for certain antitumor agents), as well as macromolecular prodrugs with polymers acting as carrier molecules [11, 12]. More recently, polymers have been used as nonviral vectors for the delivery of genetic materials for gene therapy [13].

Experimental

4-Amino antipyrine or procain, and methyl nadic anhydride were purchased from Fluka and Merck. All chemicals were analytical grade and used as received. Double distilled water was used throughout the investigations of controlled rates of drug polymers.

Synthesize of N-4-antipyrinyl methyl nadamic acid (M1) and Procainyl methyl nadimic acid (M2). [9]

0.0144 Mole of methyl nadamic anhydride was dissolved in 40ml of freshly (dioxane: di methyl formide) (10:1 vol.) in round bottom flask. (0.01mole) of dissolved 4-aminoantipyrine or procaine was added gradually as a primary amine, the mixture was stirred for 1 h at room temperature until a colored product of amic acid was obtained. The yield was recrystallized from ethanol. Table (1) shows the physical properties of M_1 and M_2.

Table (1) Physical properties of M_1 and M_2

No.	m.p ^{0}C	Color	Yield %	UV. Absorption nm
M_1	67-68	yellow	93	225,305
M_2	60-61	yellow	91	240,325

Free radical Polymerization of M_1 and M_2 to P_1 and P_2. [10]

Three grams of N-4-antipyrinyl methyl nadamic acid M_1 or procainyl methyl nadamic acid M_2 was dissolved in 10 ml of dry dioxane in a screw –capped polymerization bottle. 0.02% of the monomer weight of Azobisisobuteronitrile initiator was added. The mixture was flushed with nitrogen gas for few minutes inside a glove and firmly stopped. The clear solution was maintained at 70 ^{o}C in a constant temperature water bath for 1h. The solution was evaporated to obtaine a residue of polymer, washed the polymer with ether for several times, dried in a vacuum oven. Table (2) shows the physical properties of prepared of polymethyl nadamic acids P_1 and P_2.

Table (2) Physical properties of P_1 and P_2

No.	Softening point ^{0}C	Color	Conversion%	Swelling % at pH7	$[\eta]_{in}$=dl/g
P_1	188- 200	yellow	90	20	0.92
P_2	190- 202	Yellow	92	12	0.91

Conversion of P_1 and P_2 to their corresponding sodium salts P_3 and P_4 [10]

One gram of P_1 or P_2 was dissolved in 5ml of dioxane with 5% of NaOH solution. The salt was formed with evaporation of the solution after that the salt was washed with ethanol three times and dried in a vacuum oven.

Swelling studies

Dynamic swelling studies of P_1 or P_2 were made as follows:-

P_1 or P_2 were swollen in solution with pH 7 at 37 ℃ to determine the parameters of swelling and diffusion. Swollen gels was removed from the water bath at regular intervals and dried superficially with filter paper. Weighted and placed in the same bath.

To investigate the time –dependent swelling behavior of P_1 in solutions with pH 7, we performed dynamic swelling studies. The swelling S% is calculated from the following relation:-

$$S\% = (M_1\text{-}M_0)/M_0 \times 100$$

Where: - M0 is the mass of dry polymer at time 0.

M_1 is the mass of swollen polymer at time t.

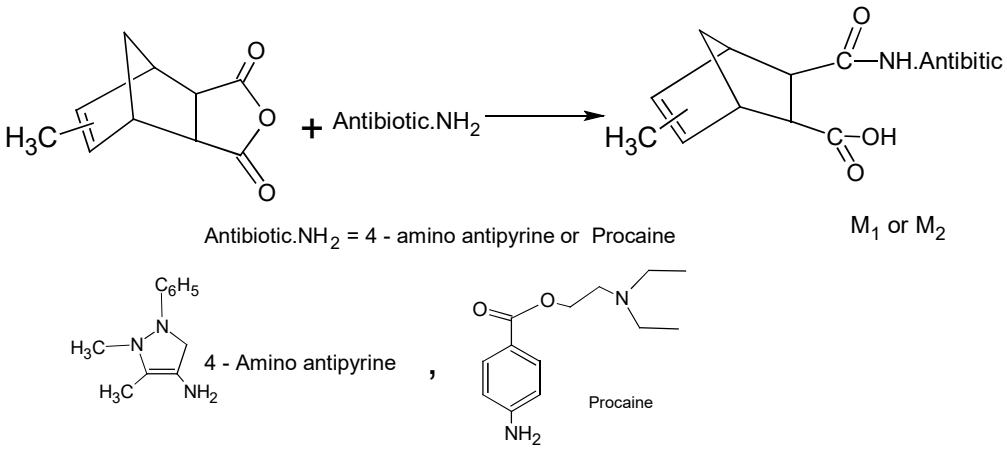
Swelling curves of polymer P_1 or P_2 in water with pH 7 at 37 ℃ shown in figure (5).

Release Studies

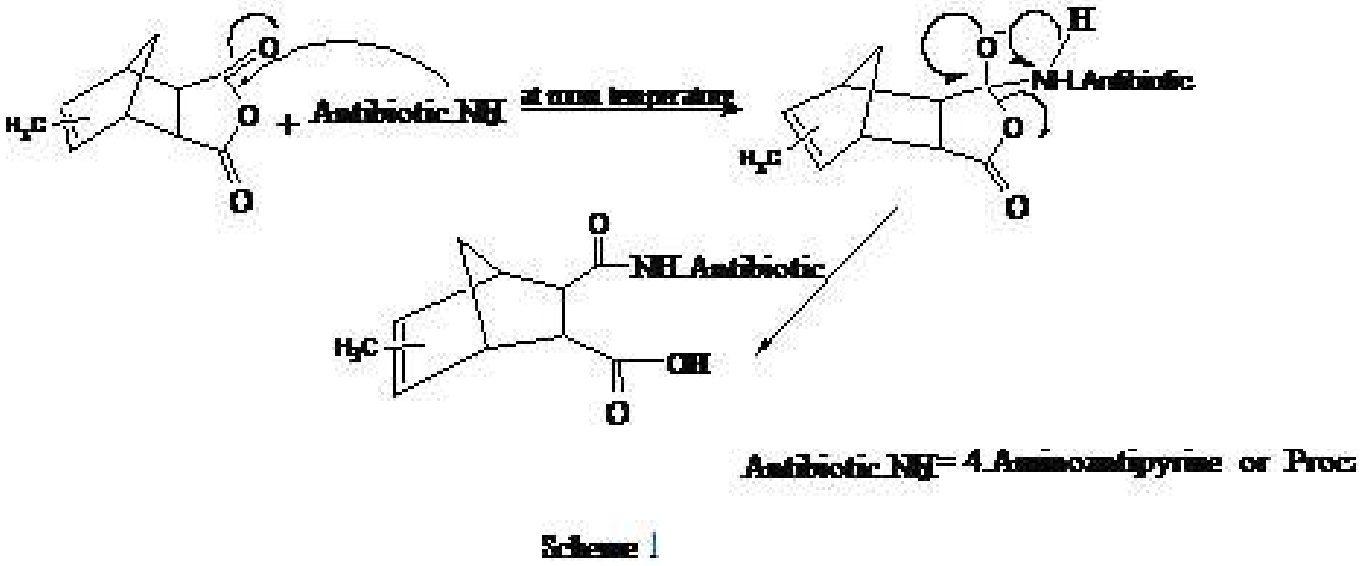
50 mg was placed in 100ml of buffer solution with pH 4 and 10 at 37 ℃ .At periodic intervals 3ml of solution containg drug polymer withdrawing and tested at λ_{max} 290 nm using Shimadzo 160A model UV-VIS spectrophotometer. The release studies were continued until the absorbance of the final solution was zero. The amount of released 4-Aminoantipyrine was quantified using appropriate calibration curve

Results and Discussion

N-4-Antipyrenyl methyl nadamic acid M_1 and Procainyl methyl nadamic acid M_2 were prepared according to the following equations:-

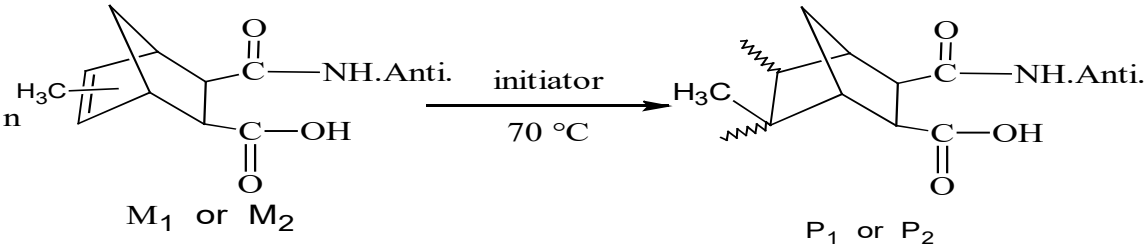


The suggested mechanism of ring opening of acid anhydride was illustrated as in scheme 1



Scheme 1

Polymerization of M_1 and M_2 monomers by using AIBN as initiator at 70 °C was described in the following equations:-



M_1 or M_2 P_1 or P_2

NH_2. Anti. = 4 - Amino antipyrinr or Procaine

FT-IR spectrum of compound [M_1] is shown in figure (1) showed appearance peaks at 3471 cm^{-1} due to υ(-NH) amide and 3061 cm^{-1} due to υ(=C-H) stretching of aromatic ring and 2964-2854cm^{-1} due the υ(CH_3,CH_2,CH), 1665 cm^{-1} due to υ (C=O) of amid and1776cm^{-1} due to υ (C=O) stretching of carboxylic acid and 1593,1500cm^{-1} due to υ (C=C) stretching of aromatic compound.

FT-IR spectrum of compound [M_2] is shown in figure (2) showed appearance peaks at 3437 cm^{-1} due to υ(-OH) of carbooxylic acid and 3066 cm^{-1} due to υ(=C-H) stretching of aromatic ring and 2958-2737cm^{-1} due the υ(CH_3,CH_2,CH), 1758 cm^{-1} due to υ (C=O) of acid and 1084 ,1153 due the υ (C-O) stretching of ester and 1712cm^{-1} due to υ (C=O) stretching of carboxylic acid and 1514,1500cm^{-1} due to υ (C=C) stretching of aromatic compound. Shoulder peak was observed for NH amide at 3260cm^{-1}.

Conclusions

The aim of this work is to synthesize drug substituted polymers that are successful for long term drug delivery and highly desirable situation because they analysis as biodegradable polymers and release over a prolong length of time and sustained released drug delivery systems that are simple and convenient to patient.

Figures (3&4) show the release of drug in different pH values at 37 ℃ .

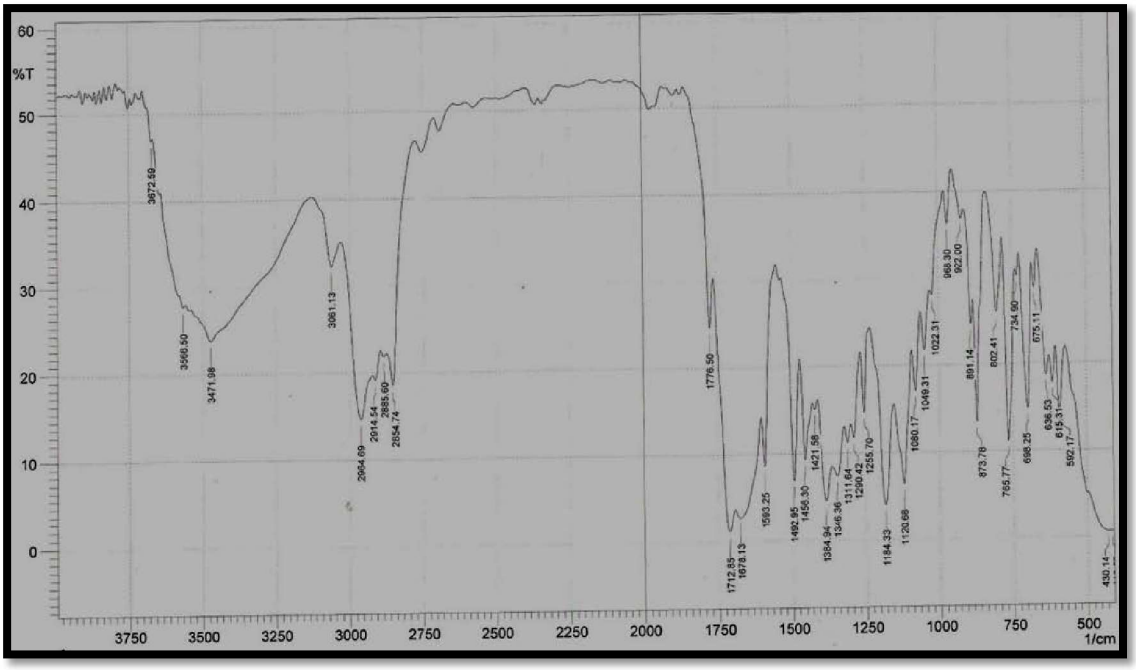


Fig. (1) FTIR spectra of N-4-antipyrinyl methyl nad amic acid (M1)

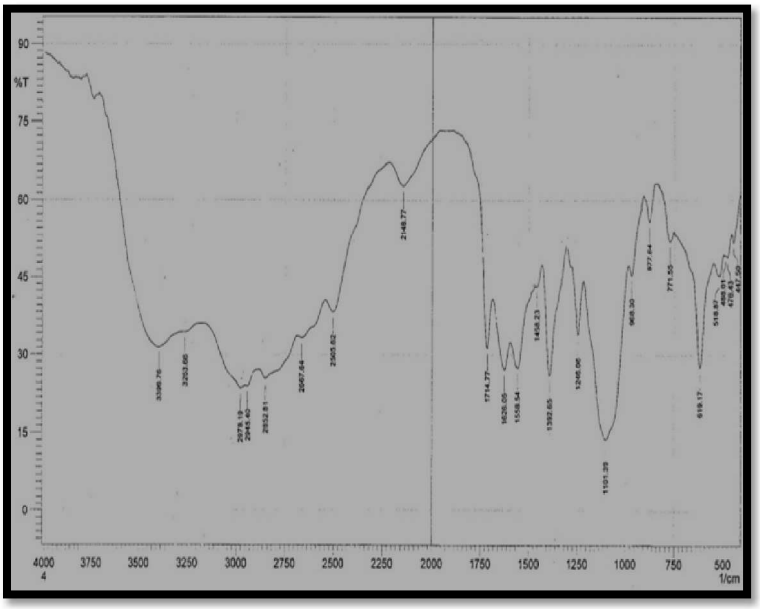


Fig. (2) FTIR spectra of Procainyl methyl nad amic acid (M2)

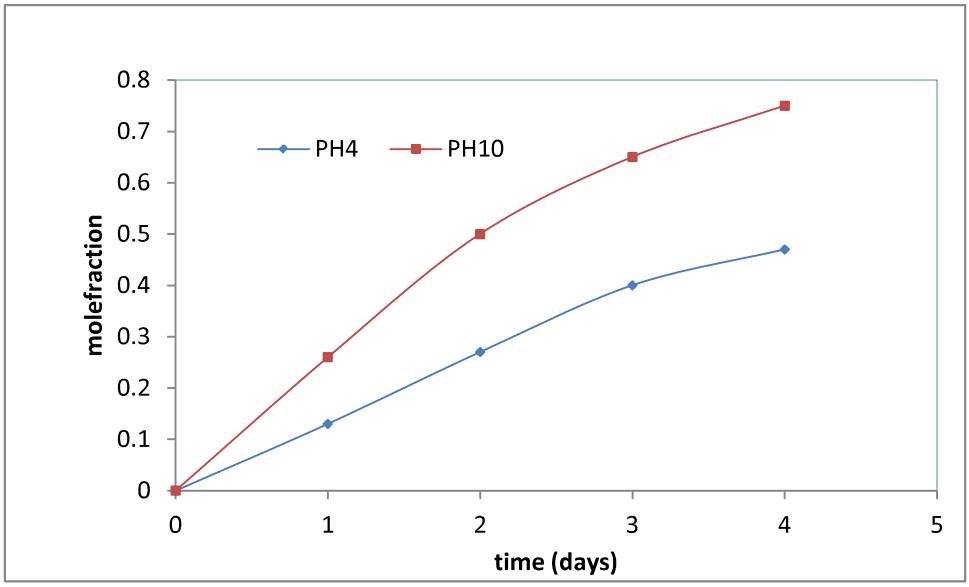


Fig. (3) Controlled release drug polymer P_1 in different pH at $37C^0$

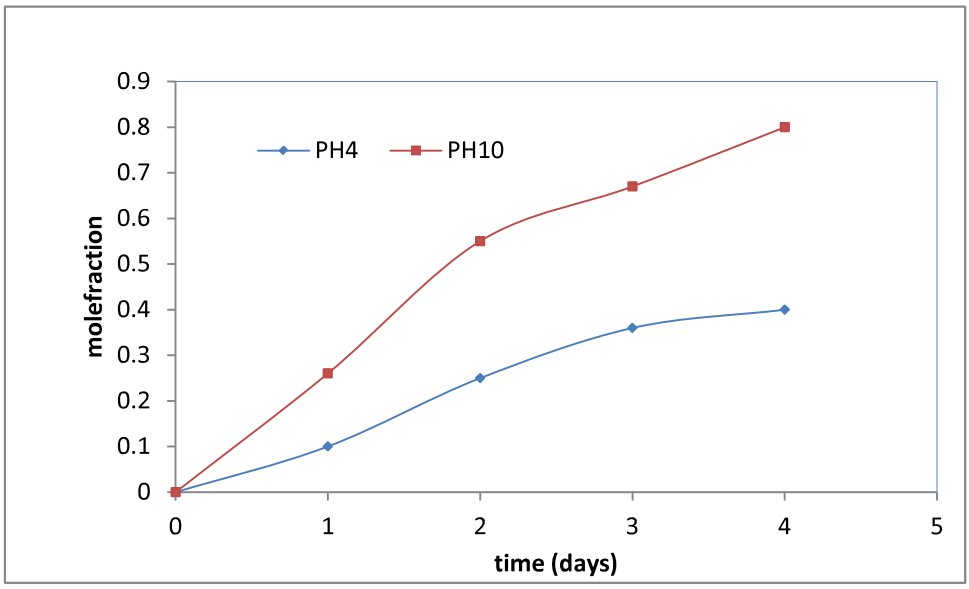


Fig. (4) Controlled release drug polymer P_2 in different pH at $37C^0$

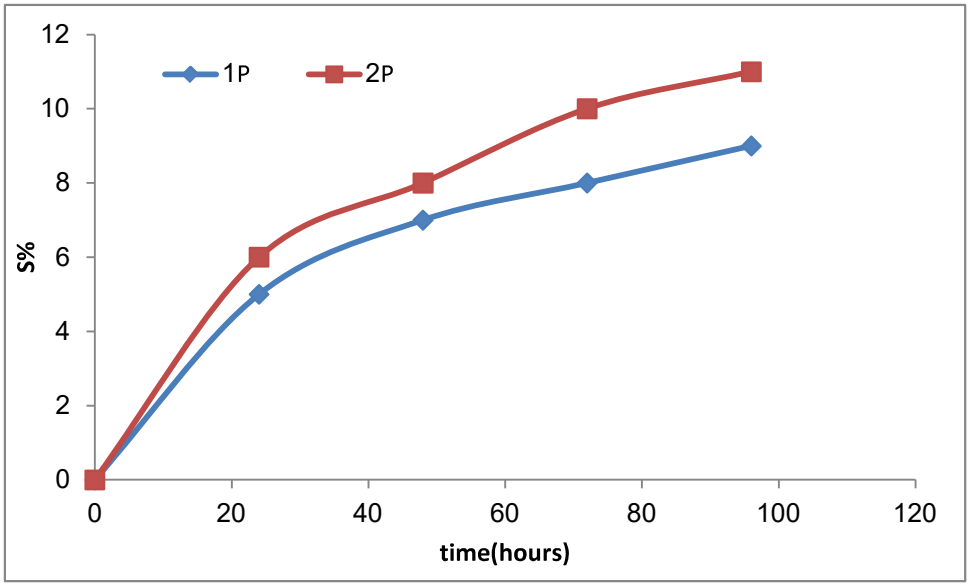


Fig. (5) Swelling curve of P1&P2 at pH 7

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