

## Synthesis of Pro Drug Polyester and Control Release

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### Abstract

Lactic acid was used as difunctional spacer could reacted with glycerol gave its corresponding ester derivative with remain the hydroxyl groups of lactate units which reacted with carboxyl group of Mefenamic acid forming ester attachment, the prepared pro drug have many development, it could enhanced the drug with easier hydrolysis through ester-ester groups with extended the arm pendant substituted drug. The action of polymeric drugs depends on hydrolytic and cleavage of the drug moiety from the polymer, this give advantages of late and sustained release of drug over long time with decrease of side effects, the modification percentage test was carried out, also it was characterized by FTIR and <sup>1</sup>H-NMR spectroscopes. Controlled drug release was deliberate by using different pH values at 37°C. Thermal stability of the drug polymer was observed, indicated the protection of drug with longer expire date. [DOI: [10.22401/JUNS.20.1.01](https://doi.org/10.22401/JUNS.20.1.01)]

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### Introduction

Some investigators have focused their attention on the preparation of bioactive polymeric materials, by bounding the drug to a polymer through covalent linking. A polymer based on a C-C backbone can resist degradation, whereas (1) it can be hydrolysis such as anhydride ester or amide bonds. The degradation is resulting in a scission of the polymer backbone (2). In order to be used in medical devices and controlled-drug-release applications, the drug polymer must be biocompatible and to be qualified as biomaterial- process and capable of controlled stability (3). Poly(esters) based on poly lactide (PL), poly glycolide (PGA), and their copolymers was used as biomaterials (4,5), Other bio- and degradable polymers include, poly(ester)s, It was used as natural polymers, particularly, modified poly(saccharide)s (4) was investigated for usability in a specific lactic acid production process based on bipolar electro dialysis/ Lactic acid has become an essential additive for flavor and preservation in a large number of industries including food manufacturing (5) its applications such as drug delivery to the production of pro drug (6), Because of this increasing demand, and also because of the more and more severe environmental constraints, more efficient lactic acid processes lead to less by-products are needed (7). The commercially used as a nano filtration membrane and by electro

dialysis (first potential integration level)(8), two molecules of lactic acid can be dehydrated to form lactide. In the presence of catalysts, lactide polymerize to either atactic or syndiotactic polylactide (PLA), which used as biodegradable polyesters. PLA is also employed in pharmaceutical technology to produce water-soluble lactates it further use in topical preparations and make up to regulate acidity and for its disinfectant and keratolytic properties (9). Lactic acid is found in milk laban, yogurt, kefir (10). Carbohydrate includes everything other than water, protein, fat, ash and ethanol (11) this means a value of 4 calories per.

Will be used for any lactic acid in calculating the food energy. Sugars into acids, unlike yeast, who ferment sugar into ethanol (12). In winemaking, a bacterial process, natural or controlled, is often used to convert the naturally present malic acid to lactic acid, Lactic acid is an organic compound with the formula CH<sub>3</sub>CH(OH)CO<sub>2</sub>H. It is a white, water-soluble solid or clear liquid that is produced both naturally and synthetically with a hydroxyl group, This higher acidity is the consequence of the intra molecular hydrogen bonding between the α-hydroxyl and the carboxylate group (13). In medicine, lactate is one of the main components of lactated Ringers solution and Hartmanns solution is repeatedly shaped even at rest and during reasonable exercise (14). The production of H<sup>+</sup> has the

same charge: "Lactate-production is not associated with a stoichiometrically equivalent of protons (H<sup>+</sup>)" (15). It is pyruvate production from neutral glucose that generates (16-23) and enhancing brain aerobic energy metabolism *in vitro* (24-25) tests for lactate are performed to determine the status of the acid base homeostasis in the body for this purpose is often by arterial blood sampling (26-27).

Mefenamic acid (MF), *N*-(2,3-Xylyl) anthranilic acid, is a non-steroidal drug. It has analgesic and antipyretic properties. Anti-inflammatory drug (30). The side effects include: headache, nervousness, vomiting, diarrhea, hematemesis (blood urine), and skin rash and swelling.

### Experimental

#### **Materials and Instruments:-**

Mefenamic acid was purchased from Samurra Company; Thionyl chloride and Triethylamine were obtained from Fluka. Lactic acid and Glycerol were obtained from Aldric. Dimethylformamide was purchased from Merck. <sup>1</sup>H-NMR spectra were recorded on a Shimadzu spectrophotometer in dimethyl sulphoxide (DMSO). The FTIR spectra were recorded by (4000-400cm<sup>-1</sup>) on a Shimadzu spectrophotometer. Melting points were determined on Callenkamp MF B-600 Melting point-apparatus. Thermal analyses were performed using TGA and DTG in Ibn Sina Center, Baghdad, Iraq. Electronic spectra measurement using CINTRA5-UV-Visible.

#### **Preparation of Mefenamic acyl Chloride A1(24-25)**

A thionyl chloride (5ml, 0.04mole) was added gradually to a mixture (2.48g., 0.04 mole) Mefenamic acid which was dissolved in 15ml of dioxane, placed in a round-bottom flask provided with condenser, the contents were stirred with a magnetic bar at room temperature. The excess of thionyl chloride was distilled off and the product was isolated and dried. Producing white powder, it was collected on a glass filter, washed repeatedly with ether giving 90%. It was immediately used in the following procedure of preparation of A3, because it is very reactive.

#### **Esterification of Glycerol with lactic acid**

**A2 (26):-** In a round bottom flask provided with condenser (14g., 0.041 mole) of Glycerol was added to (15g., 0.124mole) of Lactic acid the mixture was refluxed with stirring for 2hrs, the viscous product was obtained, washed with ether and dried at room temperature. The polymer was obtained with 89% as a colorless viscous polymer with  $\mu_{in} = 0.76$  dL/g.

#### **Substitution of Polymer A2 with Mefenamic acid chloride A1 to**

##### **A3 polymer (26)**

(2g., 0.013 mole) of prepared polymer A2, was dissolved in of dioxane: DMF mixture (5:1vol.), the mixture was heated at 60°C the prepared acyl chloride and (1ml) of triethylamine was added to dissolved (4.5g., 0.013mole) Mefenamic acyl chloride A1, the mixture was refluxed with stirring for 3hrs., The solvent was evaporated under vacuum; the product was washed with water three times, dried under vacuum oven. The yellow polymer was obtained with **conversion percentage** 72%. The softening point of the drug polymer was (180-190) °C.  $\mu_{in} = 0.81$  dL/g.

#### **Determination of degree of acid substitution (Conversion Percentage). (26)**

(5mg) of prepared drug polymer was dissolved in 2ml of 0.1 N NaOH, the solution was heated to 70°C, for 10min in a water bath, cooled and the resulting solution was titrated with 0.1N HCL to determine the excess of NaOH solution which equivalent to unreacted of mefenamic acid.

#### **Controlled drug release (27):-**

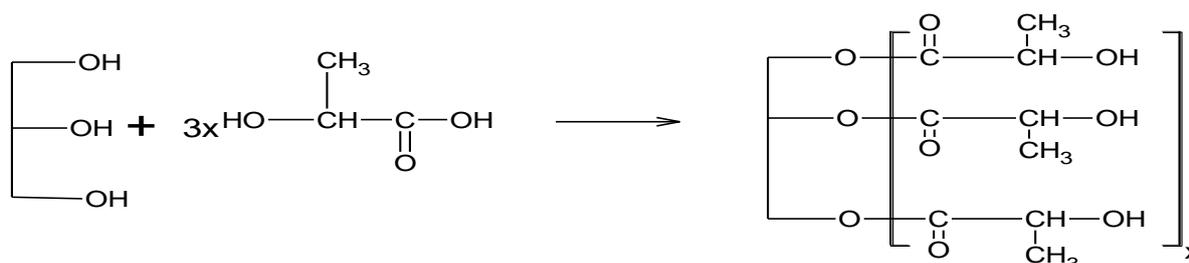
(100mg.) of dried prepared drug polymer was poured in (100ml) of aqueous buffer solution such as (phosphate buffer pH 7.4) or acidic (solution pH 1.1). The buffer solution maintained at 37°C. With stirred and (3ml) of sample was analyzed by UV spectrophotometer, it was compared with mole fraction curve which was obtained computerized under similar medium. Fig.(4), showed controlled drug release in different pH values at 37°C.

### Results and Discussion:

The main objective of the research is to synthesis and study of lactate polymers containing drug substituted groups. The work includes ester attachment.

The action of polymeric drugs depends on hydrolytic on cleavage of the drug moiety from the polymer this give advantage of delayed and sustained release of drug over time with corresponding decrease of side effect.

**Glycerol was reacted with Lactic acid produced ester polymer A2 as shown below:**



The prepared polymer A<sub>2</sub> was characterized by FTIR spectrum, Fig.(1) shows the band assigned to the terminated -OH of lactic acid at 3392cm<sup>-1</sup> due to the hydroxyl group of substituted lactic acid group, and 2974 cm<sup>-1</sup> of C-H aliphatic, 2785cm<sup>-1</sup> of methyl, 1718cm<sup>-1</sup> represented to(ester carbonyl) and 1126cm<sup>-1</sup> of C-O ester.

Fig.(3) <sup>1</sup>H-NMR spectrum of A<sub>2</sub> showed the signals at 2CH<sub>2</sub>-CO (2H) d,δ:2.8 ppm of CH-CO (1H) and δ:2.4 ppm of CH-CO (1H)S., and δ : 1.3 ppm due to CH<sub>3</sub> terminal of (3H) d, of Lactic acid, δ:4.0 ppm of O-CH(1H)Q, and The remained carboxylic acid and Lactic acid. FTIR spectrum Fig.(2) ester polymer A<sub>3</sub> showed the beak at and 3063cm<sup>-1</sup> of C-H aromatic, 1705cm<sup>-1</sup> is attributed to (carbonyl-ester) and the other absorption appeared at 1722cm<sup>-1</sup> is for carbonyl of acid and the new absorptions were appeared at 3417cm<sup>-1</sup> of NH amine of drug.

The thermal stability of prepared polymer was investigated by thermo-gravimetric analysis (TGA) and (DSC). This technique is based on measuring the weight loss as a function of time at constant temperature or as Fig.(4) a function of temperature at constant rate of heating. In the present study, the thermal stability of the prepared polymer was tested by thermo-gravimetric technique by measuring the sample weight change at a

programmed rate of heating. The change in weight was measured as a function of temperature which gave valuable information about the thermal stability of the prepared compounds. Prepared polymer was taken from under a programmed heating rate of 20<sup>0</sup>C/ min. (use Helium as inert gas in rat 20ml/min). Thus the weight-loss vs. temperature thermo-grams were recorded and analyzed. as shown in Table (1), which indicated the good thermal resistance and showed three steps of weight loss-temperature. This high thermal resistance indicated the high molecular weight of the prepared polymers with high interaction between hydrogen bonding through the polymer chain.

**Table (1)**  
**Thermal stability parameter of prepared polymerA3.**

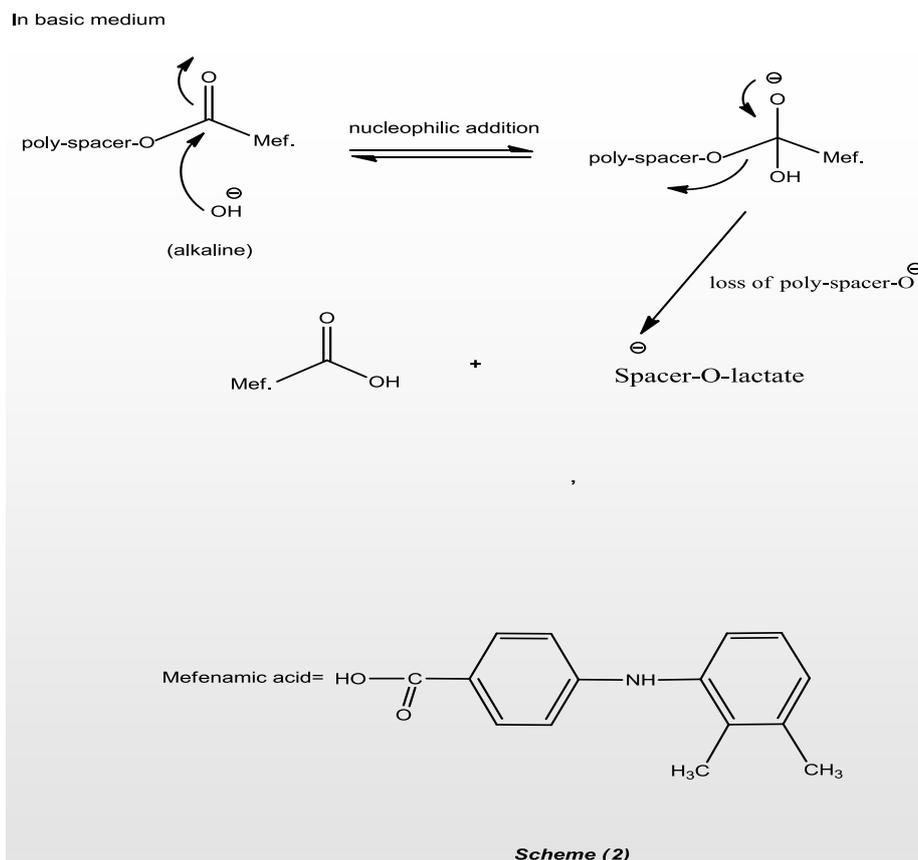
Codes No.	Temp. <sup>0</sup> C	Weight Loss%
Polyester A3	15.81	4.2791
	122.66	91.3488
	199	90

Fig.(5) showed the release profile of drug release (mole fraction) versus time.

The controlled release rates was studied as drug polymers which could be hydrolyzed in

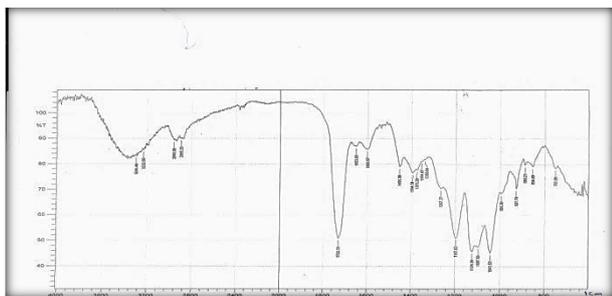
basic and acidic medium due to ester-ester bonds.

In this work it was concluded that the presence of difunctional spacer group was inserted between the drug and polymer backbone through ester group which could easy hydrolysis as a pendant group, with increasing of satiric effect of polymer chains., that the extended side arm of Glycerol with suitable spacer di-functional such as Lactic acid (26) with Mefenamic acid as a drug. In basic medium, the rate of hydrolysis is higher than acidic medium this is due to the presence of  $\text{OH}^-$  in alkaline, which acts as a good nucleophilic attack to  $\text{H}^+$  bonded to oxygen atom of ester as shown in Scheme (2). The spacer effect appeared carbonyl group with respect to water, and the  $\text{H}_2\text{O}$  is faster.

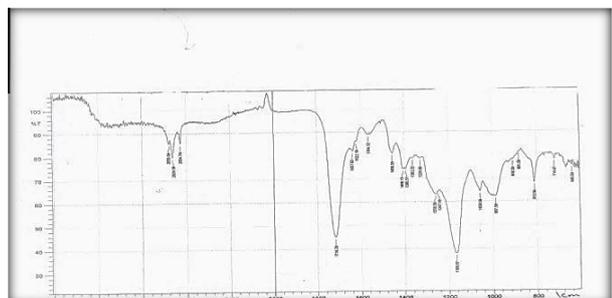


In acid medium

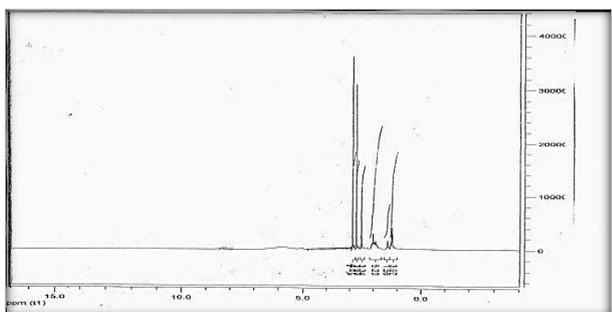
**Scheme (2)**



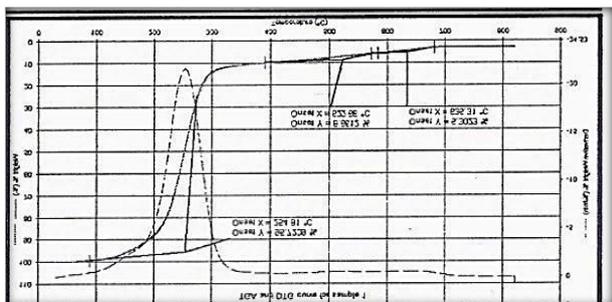
**Fig.(1): FTIR spectrum of A2.**



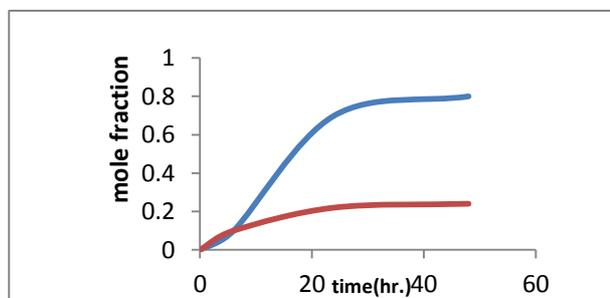
**Fig.(2): FTIR spectrum of (A3)**



**Fig.(3): HNMR.**



**Fig.(4): TGA of A3.**



**Fig.(5): Drug release of A3 at pH 1.1 and 7.4 at 37°C at 400nm.**

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