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Synthesis and Modification New Prodrug Polymers Based on Glycerol with Adipic Acid

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Abstract

The importance of smart polymers is rising daily and polymers undergo for a large reversible reactions due to their chemical and physical changes in the environment conditions pH, temperature, light and phase transition, Also the smart polymer advantages: biocompatible, strange, tough to color and maintain stability of due drug, in addition to the term (smart polymer) is refer to a different compounds that can change their color or shape in reaction to their surroundings. All possible studies were performed such as: intrinsic viscosity, swelling measurement and controlled drug release of drug also thermal analysis prodrug polymer were done.

Keywords: Synthesis, Characterization, Prodrug, Ampicillin, Propranolol

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INTRODUCTION

The esterification is one of the chemical reactions that can be used for organic,bio organic, medicine, food and pharmaceutical industries [1], [2]. The direct esterification (Fischer esterification) is a condensation reaction between acid and alcohol through finding a catalyst for ester synthesis [3]. The glycerol has a greatest attention and through esterification reaction with ampicillin prodrug polymer bonded to the glycerol through an amide bond.

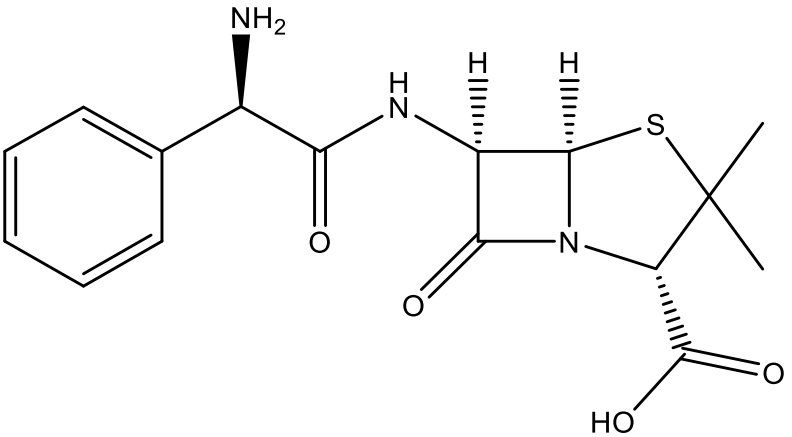


Figure 1. Structure of Ampicillin

Generally, it is used for reducing pain, headache [4]. Also, for treatment (GI) toxicity as Anti-inflammatory drugs (NSAIDs). In spite of the mechanism action of a polymer prodrug is regard unclear, and the choosing of carrier is depend on the molecular weight, also on the favor attachment should be a valuable, and a high attention was taken a part for the preparation also the properties of pharmacological active polymers [2], [3].

The paper deals with synthesis propranolol as another prodrug polymer were synthesized too. It was one of the medicines of beta – blocker that can be used for treatment tremors, angina and hypertension [5], [6]. Many synthetic polymers were in active biologically, and the others were toxic and a wide range of polymers were used for therapy activities [7].

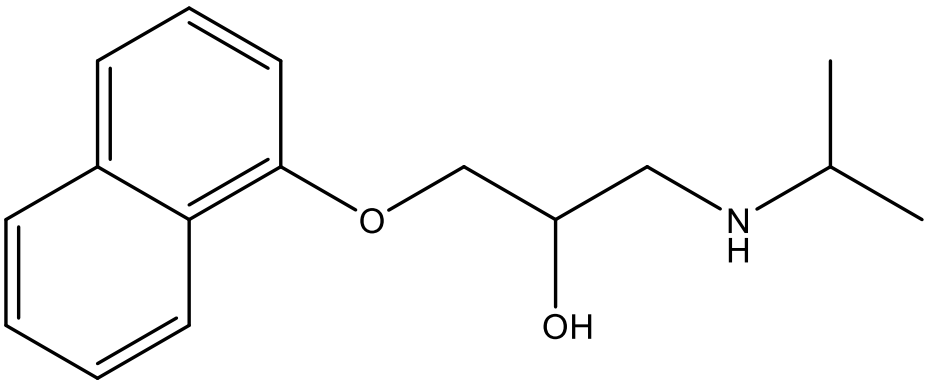


Figure 2. Structure of Propranolol

The term (prodrug) or (codrug) indicated to more therapeutic compound that bonded through a covalent chemical linkage [10].

Propranolol was another prodrug polymer studied in this paper too, It was one of the medicines of beta-blocker that can be used for treatment tremors, angina and hyper tension. Many studies were marked to be the best for using the propranolol in treatment risk of neck, head, colon and prostate cancers [9], [10].

MATERIALS AND METHODS

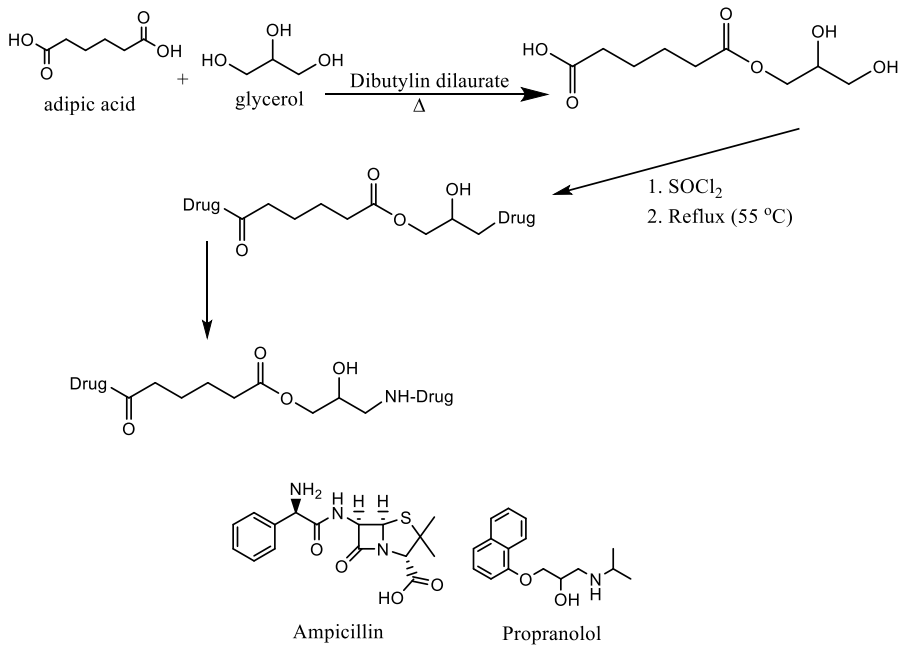
Experimental

Materials and Instruments

Ampicillin and propranolol were obtained from Samarra company. Glycerol and Adipic acid were obtained from CDH, BDH, respectively while Thionyl chloride was purchased from Alfa. The FT-IR spectra was recordered by (4000-400 cm-1) on a Bruker spectro photometer and 1H-NMR spectra were recordered by a Bruker Spectro photometer in dimethyl sulphoxide (DMSO). Melting points were calculated through using melting point apparatus. Viscosity, swelling and solubility results were calculated through this paper. Thermal analysis were determined by TGA and DSC in Iran: TGA, DSC BAHR, (Germany).

Method

Esterification of glycerol and Adipic acid in a round bottom flask provided by condenser (10 gm) of glycerol was added to (10 gm) of adipic acid to obtain the mixture, and it was refluxed with stirring for 1 hour after addition (1 gram) from each drug (Ampicillin and Propranolol) and 10 drops of thoinyl chloride were added to the mixture were refluxed again for 1 hour, the products were collected and washed many times by diethyl ether and lastly dried at room temperature.



Scheme 1. Synthesis of prodrug polymers (P1, P2)

RESULTS AND DISCUSSION

The suggested structures for an amide prodrug polymer were determined by spectrophotometric methods.

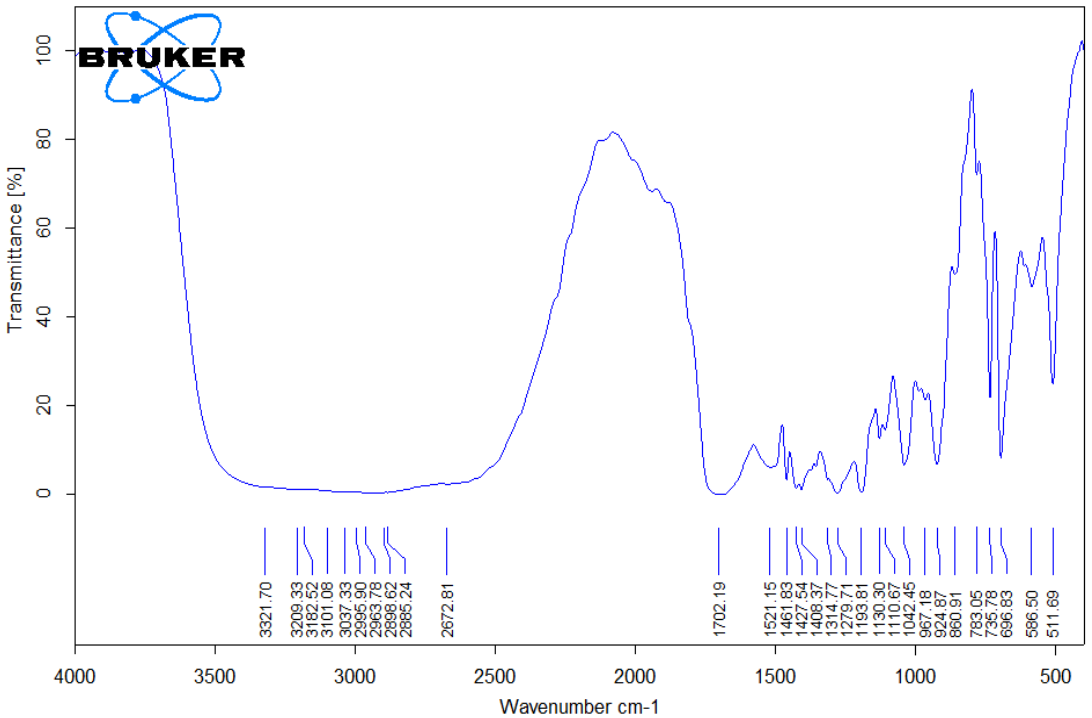


Figure 3. Structure of Ampicillin

While for FTIR of (P1) polymeric prodrug there are several peaks, first peaks for OH stretching (3321.70)cm-1, and (2898.62) cm-1 is related to CH group lastly (1702.19) cm-1 as indicated for an amide group.

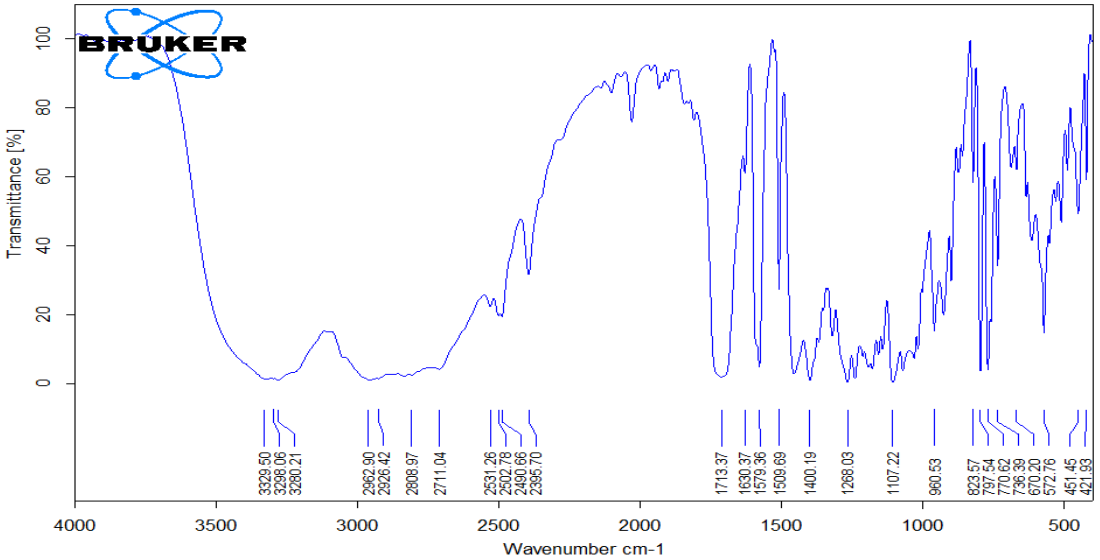


Figure 4. Structure of Propranolol

Lastly, for (P2) polymeric prodrug there are different peaks, first peaks for OH stretching (3329-3298) cm-1, (2962-2926) cm-1 is related to stretching CH group lastly (1713.37) cm-1 as indication for an amide group.

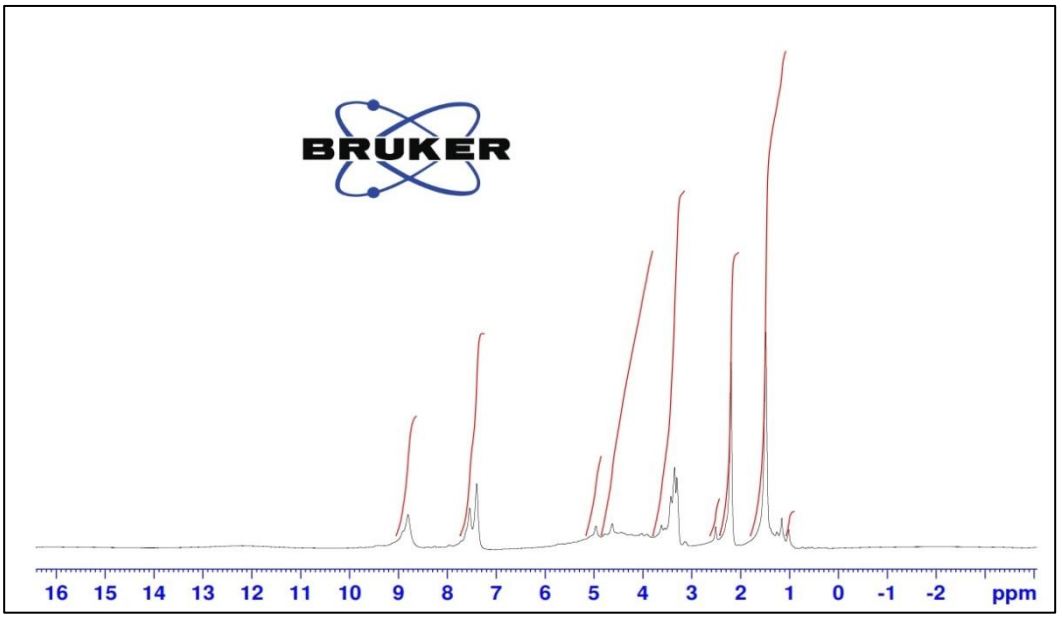


Figure 5. Structure of Ampicillin

Table 1. Chemical shift for (A55)

Protons	Chemical shift ppm
CH3	1-1.5
CH2	2
DMSO	2.5
	3.80
H- aromatic ring	7.8
Carboxylic group	9

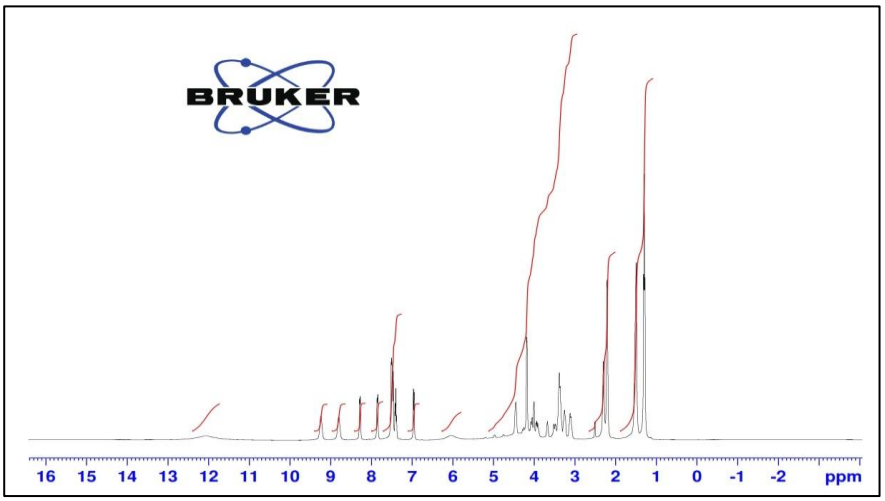


Figure 6. Structure of Propranolol

Table 2. Chemical shift for (A58)

Protons	Chemical shift ppm
CH3	1.3-1.5
CH2	2
DMSO	2.5
H- aromatic ring	7-8
amide group	8-9

Swelling and intrinsic Viscosity of prodrug polymers

From the result of the table above the value of intrinsic viscosity for the ampicillin polymeric prodrug is higher than other polymers (Propanalol), also the high value of swelling percentage for same polymeric prodrug ampicillin as compared with the others.

Table 3. Swelling and intrinsic viscosity of polymers

Polymers	Intrinsic viscosity η dl/g	Swelling %
P1	13.8	0.85
P2	10.6	0.76

Study of drug release of prodrug polymers

The active group of prodrug polymer is an ester bond (Ampicillin), and this bond can be hydrolyzed inside of the human body through enzymes or by hydrolysis in different media acidic and basic according to the suggested mechanism.

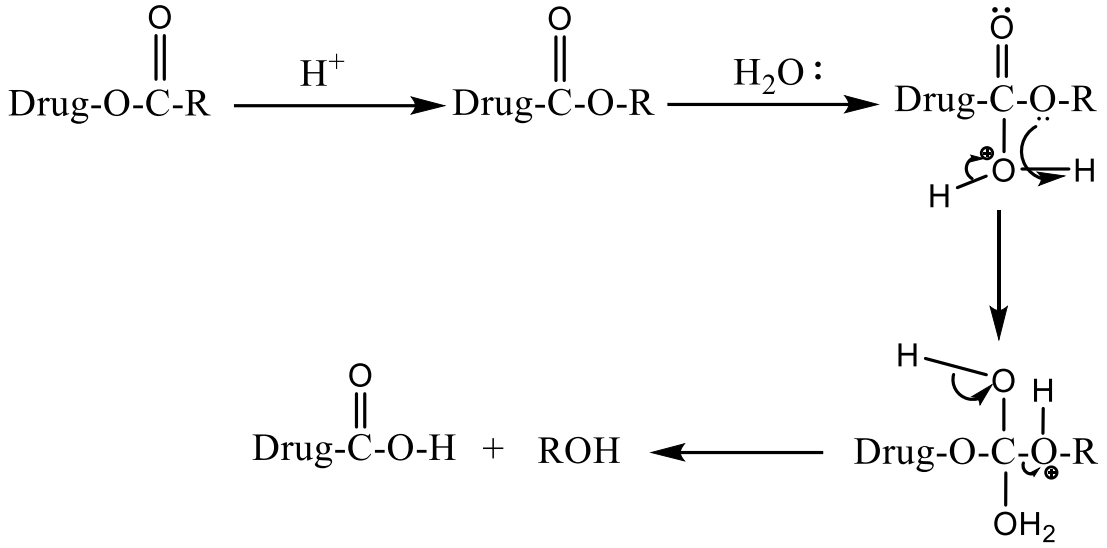


Figure 7. Hydrolysis mechanism of acidic medium

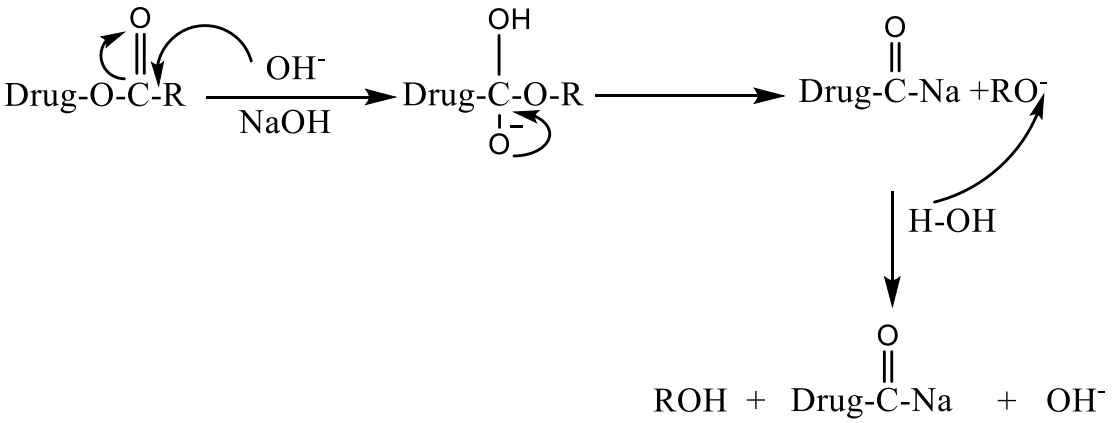


Figure 8. Hydrolysis mechanism of basic medium

The hydrolysis of ampicillin prodrug polymer in acidic or basic medium is regard ester drug and hydrolysis in stomach to indicate for negative big effect on the healthy, also ampicillin contains carboxylic group (as an acidic character) lead to convert (ampicillin) to prodrug polymer and the hydrolysis of ampicillin in basic medium without side effect according to:

Table 4. Controlled drug release of prodrug polymers (P1, P2) at differen**t pH (2,7,8)**

pH= 2.0		
time/day	**P1 nm**	**P2 nm**
1	0.271	0.231
2	0.251	0.251
3	0.281	0.262
4	0.311	0.288
pH= 7.0		
time/day	**P1 nm**	**P2 nm**
1	0.428	0.255

2	0.452	0.298
3	0.562	0.322
4	0.661	0.441
	pH= 8.0	
time/day	**P1 nm**	**P2 nm**
1	0.556	0.551
2	0.661	0.572
3	0.722	0.693
4	0.882	0.811

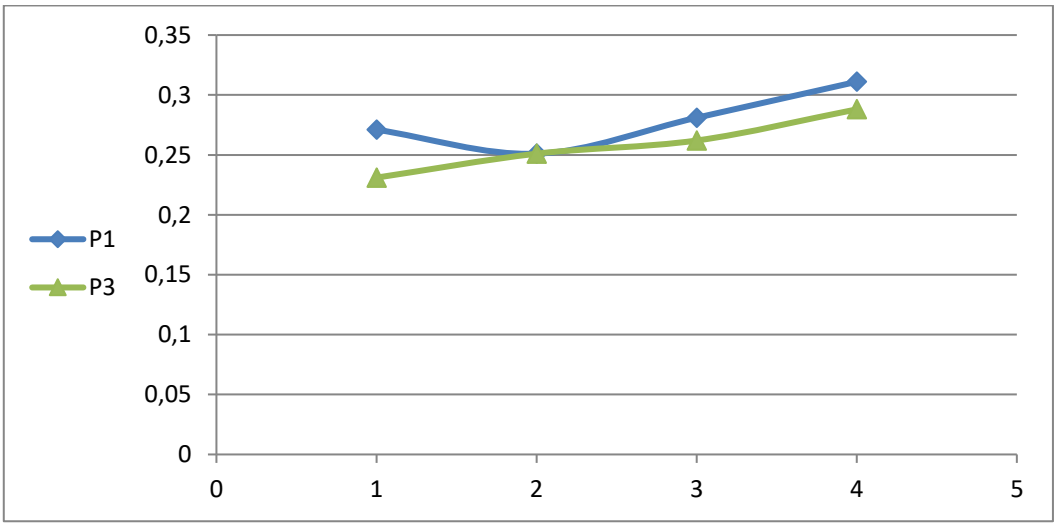


Figure 9. Controlled drug release at pH =2 for prodrug polymers (P1, P2)

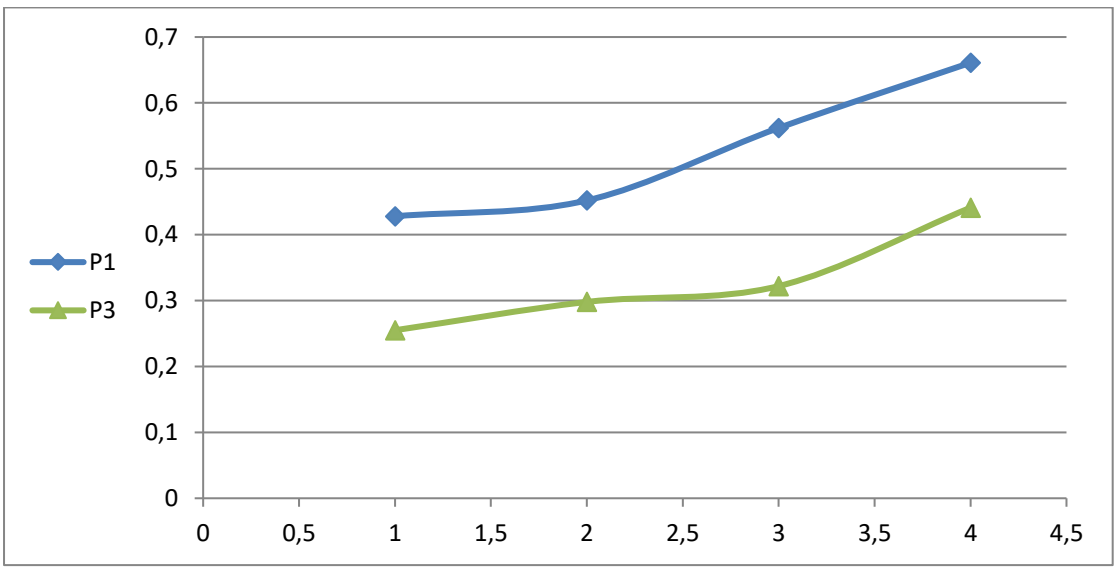


Figure 10. Controlled drug release at pH =7 for prodrug polymers (P1, P2)

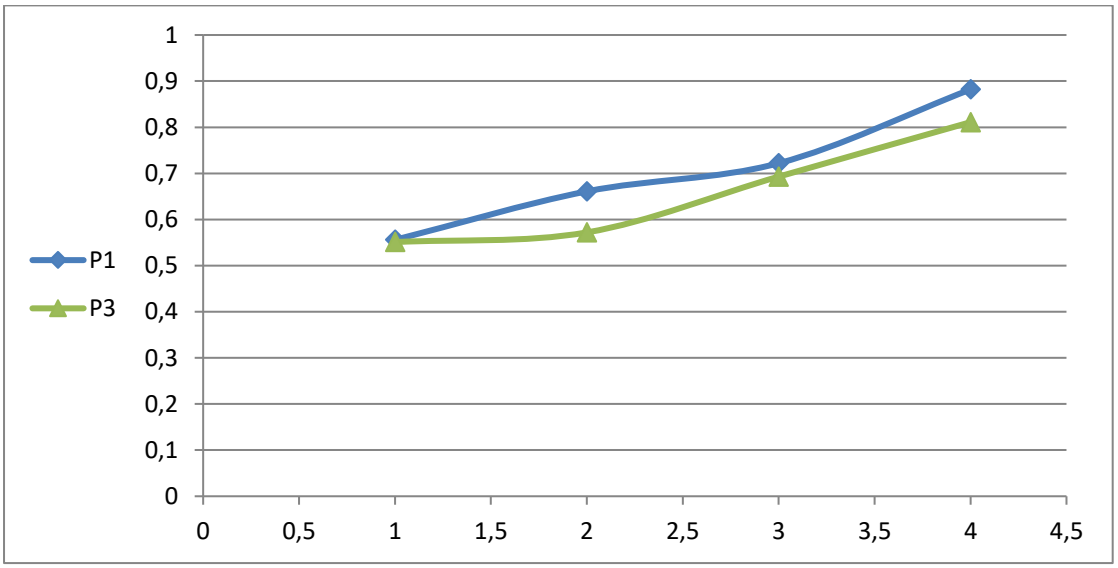
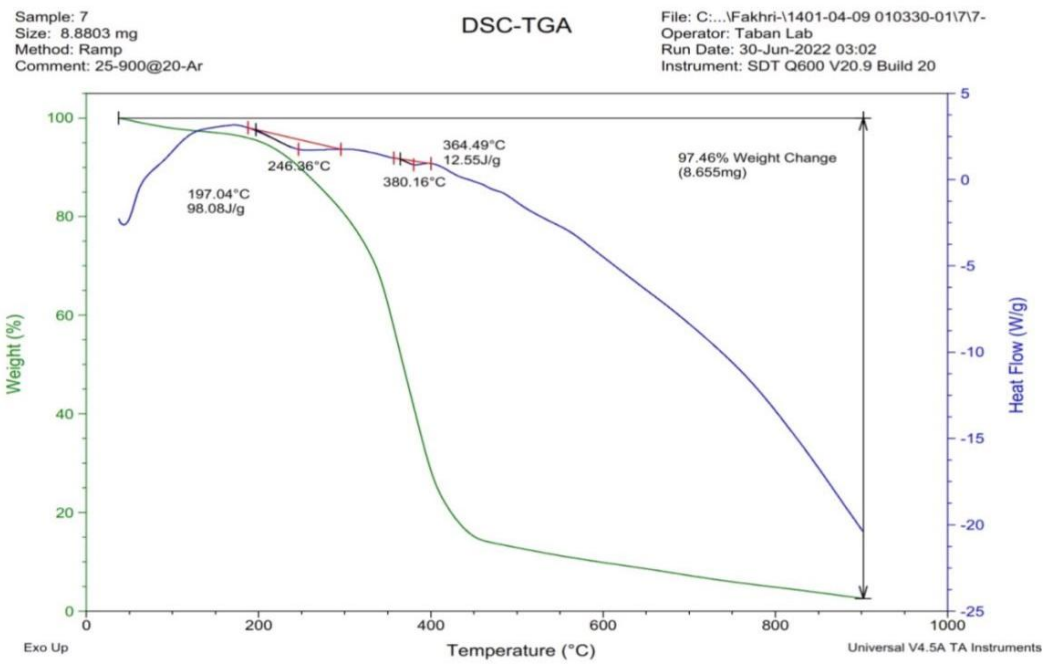


Figure 11. Controlled drug release at pH =8 for prodrug polymers (P1, P2)

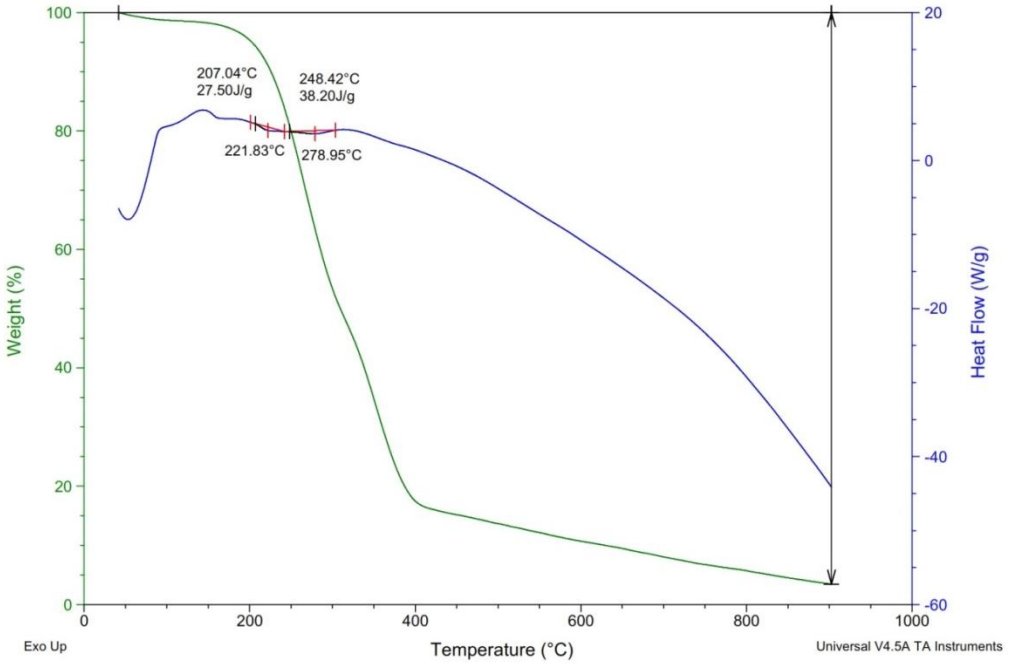
Thermal analysis of prodrug polymers

Differential Scanning Calorimetry (DSC) is widely used for examination of polymeric materials and to diagnosis the thermal shift such as glass transition, crystallization temperature and melting point, all these thermal shifts were used to compare materials and there compositions [11]-[13]. While thermo gravimetric analysis (TGA) is related to the change of weight with the temperature from thermal analysis resistivity of propanalol shows a good thermal stability at (360C) [14], as compared with ampicillin prodrug polymers, while the thermal stability in high temperatures for prodrug polymers is due to [15]:

1. Mechanical change of prodrug polymers
2. The physical change in polymer such as distortion of shape with temperature



Scheme 2. Thermal analysis of prodrug polymer P1



Scheme 3. Thermal analysis of prodrug polymer P2

CONCLUSION

The synthesis of these polymers prodrug (Ampicillin and propranolol) was done by reflux method and all polymer results were characterized by different techniques such as FTIR, H-NMR, viscosity and swelling percentage indicated for high value of ampicillin as compared with the other polymers, also solubility of polymers in water generally gave good results while the control drug release for these polymers was shown through different pH (2,7,8) and lastly the thermal analysis for those polymers pointed to good thermal stability toward high temperatures.

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