

ORIGINAL RESEARCH ARTICLE

Synthesis and Characterization New Polymeric Drugs and Study Their Controlled Drug Release

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ABSTRACT

Prodrug based on polymers are pictured macromolecules and these prodrugs performance unique angle to raise the solubility and pharmacokinetics and pharmacological properties. According to their benefits as anticancer drugs, the highlights focused on the synthesis of prodrug polymers and their applications in medicine field, So these polymers having degradable amide bonds linked to paracetamol and ester bonds bounded to ciprofloxacin as a material for drug delivery .

The characterization of the resulting products were carried by FT-IR, ^1H – NMR , XRD, thermal analyses (TG, DTG, DTA, DSC) swelling ratio , controlled drug release and Anti-oxidant as an application of these polymers.

Keywords: Synthesis, Chitosan , macromolecules , Controlled drug release

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1. Introduction

Macromolecules like polysaccharides, proteins and peptides could be utilized as carrier in order to form macromolecular prodrugs^[1] . A prodrug is a frame of a drug that be inactive during it's delivery to the site of action and it's activated by a specific condition in the targeted site. The conjugation of a drug with a polymer so called polymeric prodrug^[2]. Chitosan is an eco-rich polysaccharide after cellulose in nature and in exoskeleton of insects, arthropods and crust oceans^[3] as stated by the presence of several derivable groups including hydroxyl, carboxyl and amino groups on the molecular structure, so polysaccharides are hydrophilic in nature and form non-covalent bonds with biological tissues^[4] .

Chitosan take the notice of the biological functions such as: biodegradability, biocompatibility, bioactivity and low toxicity^[5]. Phthalic anhydride is a cyclic pattern with no – end ring molecule and it's necessary tool for bioconjugation chemistry^[6]. Phthalic anhydride is regard heterocyclic substrate of reactions and it's name (2-Benzo furan – 1,3 dione) as an organic compound with the chemical formula $\text{C}_6\text{H}_4(\text{CO})_2\text{O}$ colorless powder and acidic odor ^[7].

Drugs:

Paracetamol act's one of the popular medication commonly used for treatment pain, and reduction of high body fever. Paracetamol chemical formula ($\text{C}_8\text{H}_9\text{NO}_2$) and it's name (N (4 – hydroxyl phenyl acetamide) also paracetamol has a free phenolic group (OH) ^[8]. Paracetamol is a well – known drug for analgesic and anti – inflammatory activity, so it's a class of aniline analgesics ^[9].

Ciprofloxacin is one of an important and general clear of β – lactamase enzyme which hydrolyze the β – lactam antibiotics. Ciprofloxacin is a broad spectrum antibiotic that can be utilized for treatment infections caused by β – lactam resistant bacterial infections ^[10]. Ciprofloxacin is faintly yellowish to light yellow crystalline substance and it's molecular formula ($C_{17}H_{18}FN_3O_3$)^[11].

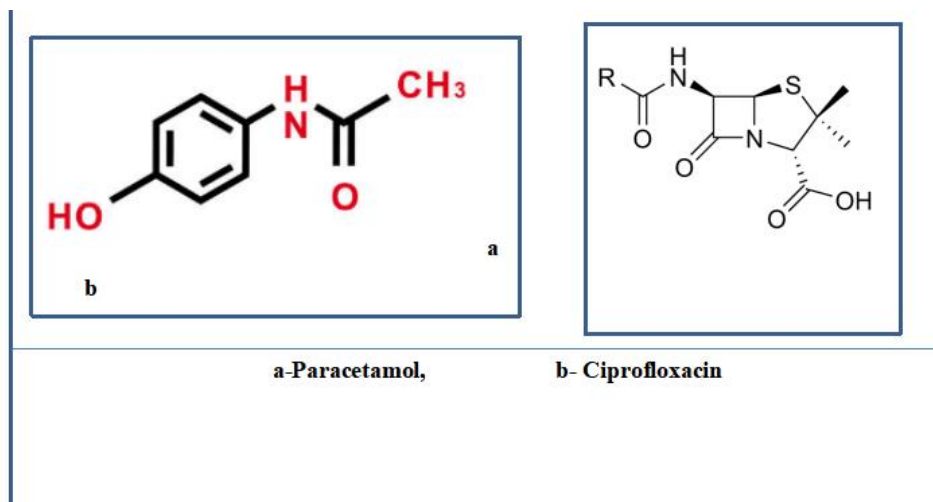


Figure 1. Chemical Structure of Drugs

2. Materials and Methods

2.1. Materials

Table 1. Chemicals and their purities

Chemicals	Company	Molecular weight	Purity %
Chitosan	CDH	$C_{56}H_{103}N_9O_{39}$	98
Ciprofloxacin	Sammarra company	$C_{17}H_{18}FN_3O_3$	99.9
Paracetamol	Sammarra company	$C_8H_9NO_2$	9.99
Phthalic anhydride	Fluka	$C_8H_4O_3$	99.5
Sulpheric acid	Alfa	H_2SO_4	98
Thionyl chloride	Alfa	$SOCl_2$	98

2.2. Measurement Techniques

2.2.1. Infrared Characterization

The apparatus that used for infrared spectroscopy characterization is SHIMADZU the acquisition between (4000 – 400) cm^{-1} as a wave number and the number of scans are(15) .

2.2.2. Proton Nuclear Magnetic Resonance (1H -NMR) Characterization

NMR spectrums were recorded by an a Bruker Biospin GmbH spectrometer and samples were dissolved in DMSO – d_6 as a solvent.

2.2.3. X - Ray diffraction (XRD) Characterization

X- Ray diffraction is an effective way to study the crystallinity of the polymers and the spectra was obtained by using (Drbenyamin Instrument Co, Ltd, Iran) with Cu, K_{α} radiation source and the 2θ value ranging from (10° – 80°) and the scanning rate was (1 sec) all results were obtained by @ 2024 PAN analytical B.V. computer program.

2.2.4. Thermogravimetric and Differential Thermal Analyses

Only DSC analysis was done by using Netzsch proteus software and the temperature range was (20-100 C°) for each (5minute) for both (P1 , P2) polymers. The differential thermal analyses techniques (TG, DTA, DTG) were used for both prodrug polymers (P1, P2) through multi-tasking software controlling the various modules and (2 mg) of the sample was taken and the temperature range was (10-80C°).

2.2.5. Swelling Ratio

Swelling ratio results of both polymers (P1,P2) were characterized by uv-visible spectrophotometer (200-700 nm) and an ostwald viscometer was used to carry the test of viscosity of polymers at (37 C°) in distilled water as a solvent .

2.2.6. Controlled Drug Release

The drug release of produced polymers (P1,P2) was done by using uv- visible spectrophotometer at constant temperature (37C°) in a buffer solution (PH =7.4) .

2.2.7. Antioxidant application of polymers

The Antioxidant activity was determined by DPPH radical scavenge and the sample concentrations (2.5 , 1.25 , 0.625 , 0.3125) mg/ml were added in cultured walls and incubated on the plates for 24 hour, later the plates were washed with distilled water and crystal violet dye was added into each well and incubated again.

2.3. Method

2.3.1. Synthesis of Prodrug Polymer (P1)

Weight (0.4 gm) of phthalic anhydride through a sensitive balance and dissolved in a beaker containing (25ml) of distilled water and (10 drops) of NaOH (20%), also addition (0.4 gm) of chitosan was dissolved in a mixture of (glacial acetic acid) with distilled water totally (25 ml) as a volume of the mixture. Then (15 ml) of H₂SO₄(1N)^[12] was added to the mixture as a catalyst , so thionyl chloride (3 drops) were added to mixture both solutions were heated at (60 C°) with a magnetic stirrer (6000 rpms) through refluxing process for one hour, after the first reflux process completion, the addition (0.5 gm) of paracetamol was done and the reflux was repeated again. The mixture was filterated and the washing of products by diethyl ether was carried for many times lastly, the collection of product as a sample was finished .

2.3.2. Synthesis of Prodrug Polymer (P2)

(0.4 gm) of phthalic anhydride was dissolved in (25 ml) of distilled water and (10) drops of (20%) NaOH was used to complete it's solubility, then (0.4 gm) of chitosan was dissolved in a mixture (25 ml) contain's both of glacial acetic acid and distilled water, then (15 ml) of H₂SO₄ (1N)^[13] was added as a catalyst to the mixture, so (3 drops) of thionyl Chloride were mixed and then the mixture was heated at (60 C°) for one hour by a reflux process with a magnetic strirrer (60000 rpms), after first reflux process completion, the addition of (0.5 gm) of ciprofloxacin was done and the reflux was repeated again, then the product was filterated and washed by diethyl ether for many times lastly, the collection of product as a sample was carried.

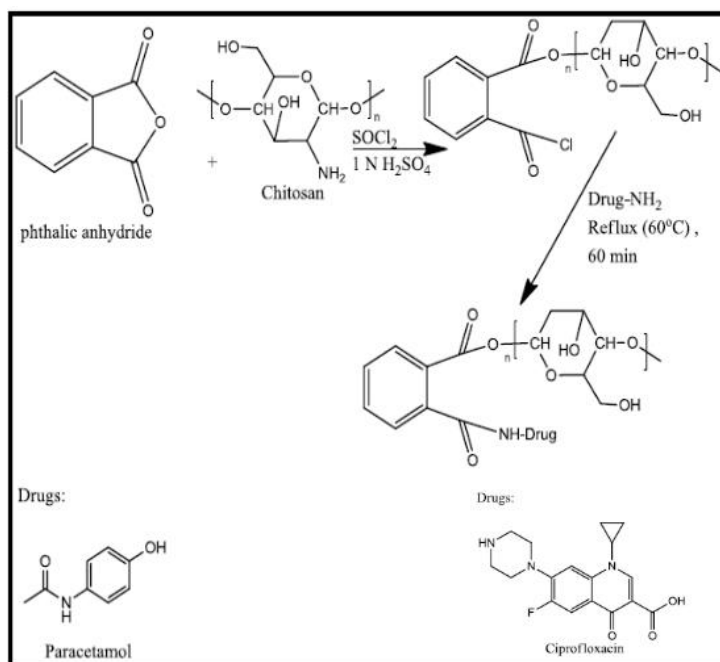
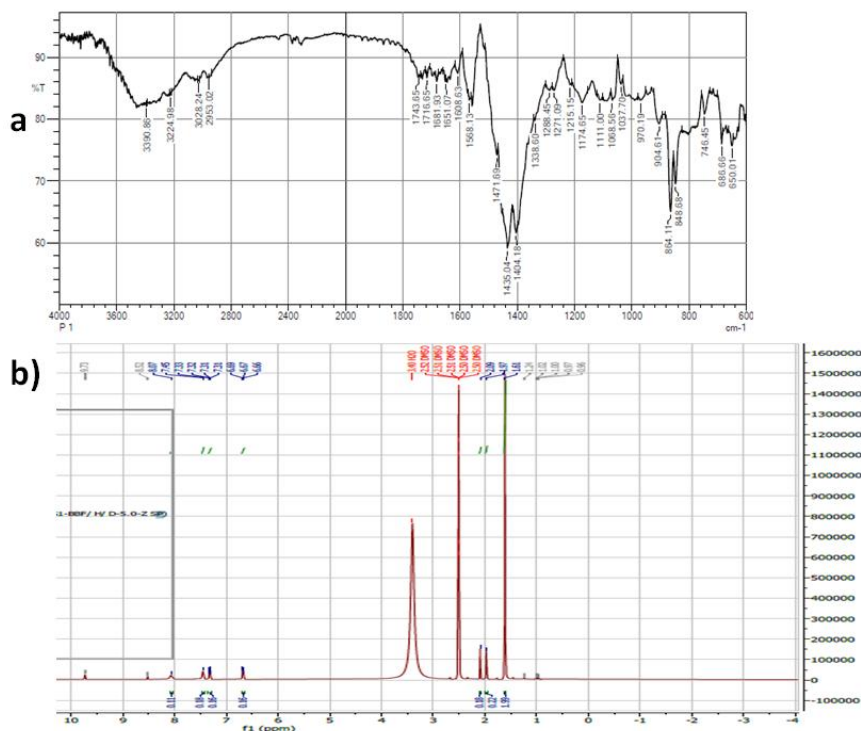


Figure 2. synthesis of prodrug polymers (P1 , P2)

3. Results and Discussion

3.1. Spectroscopic Characterization

The prodrug polymer (P1) as a product , it's weight (5gm) , deep green color and FT-IR spectrum was shown as in the figure(2): (3390 cm^{-1}) ν (N-H) of an amide group, (1271 cm^{-1}) ν (O-H) and (1681 cm^{-1}) ν (C=O) of an amide (1568-1338 cm^{-1}) for Ar-(C=C) and (1271 cm^{-1}), ν (C-N) (13). ^1H -NMR of (P1) appear these signals: (1.61 – 1.97 ppm) for CH₃ resonance, (2.50 ppm) for DMSO – d₆ as a solvent, (3.40 ppm) for methoxy protons (OCH₃) , (6.66 – 8.07 ppm) for protons of an aromatic ring, and (9.73 ppm) is for proton of an amide group [14].



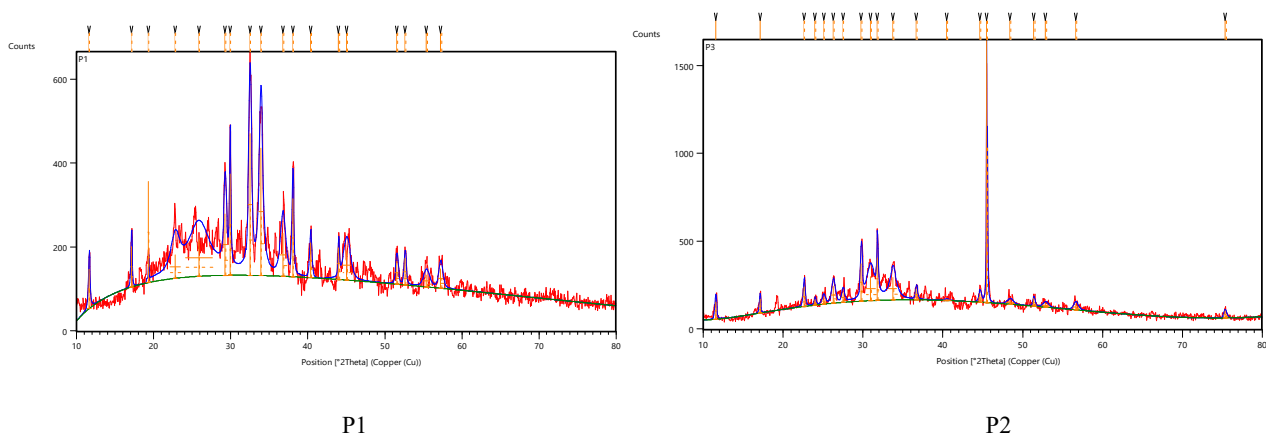


Figure 5. XRD analysis of P1 and P2 prodrug polymers

Crystallinity Degree (CI) :

$$CI (P_1) = \frac{38^\circ - 22^\circ}{38^\circ} \times 100$$

$$CI P_1 = 42.1\%$$

$$CI (P_2) = \frac{48^\circ - 22^\circ}{48^\circ} \times 100$$

$$= 54.1 \%$$

3.3. Thermal analyses of Polymers

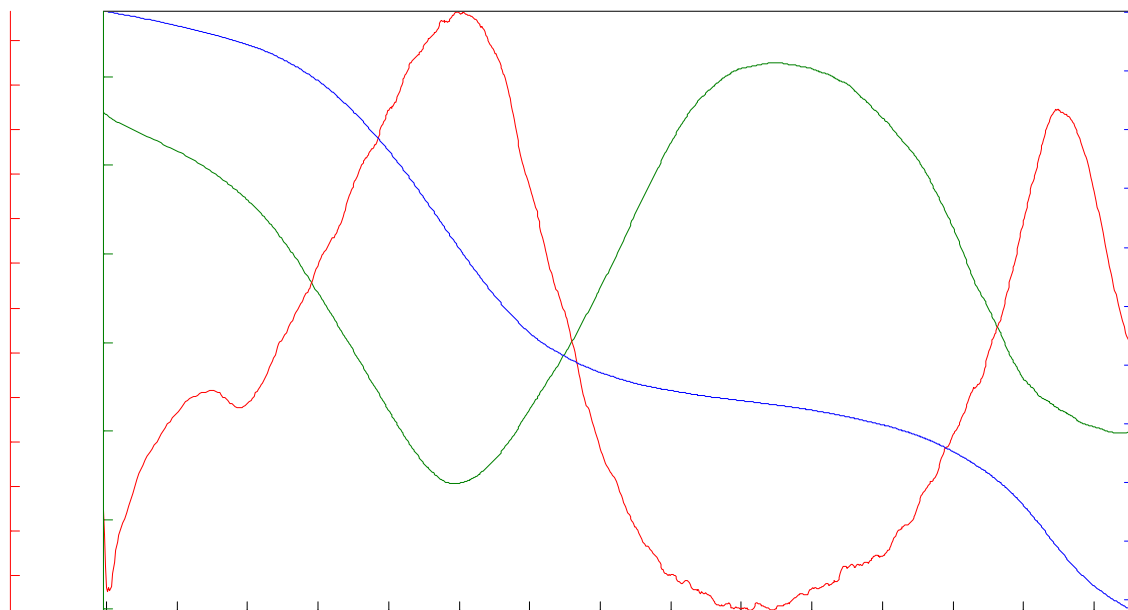


Figure 6. Thermal analyses (TG , DTA, DTG) of prodrug polymer (P1)

TG results according to the figure (5) show the prodrug polymer (P1) undergoes thermal degradation beginning at 40C°,50 C°,80 C° and totally mass losing (14%) chitosan as a polysaccharide has a high affinity for water by that the reaction is endothermic and generally refer to water evaporation and the strength of the interaction between water and polymer was melted by their capacity to hold water . [18]

While DTA analysis of prodrug polymer (P1) the temperature of initial drop between (35, 45, 65 and 85 C°) with weight loss (93%, 86%, 100%, 85%) and the reaction is endothermic may be attribute to the

evaporation of water absorbed in the inner chitosan chains^[19], for DTG analysis of prodrug polymer (P1) (40, 53, 80 C°) are matched to weight loss (97%, 90%, 87%) and these main stages: water evaporation, active and passive pyrolysis. ^[20]

Another prodrug polymer (P2) thermal analyses results were shown as in the figure (6) :

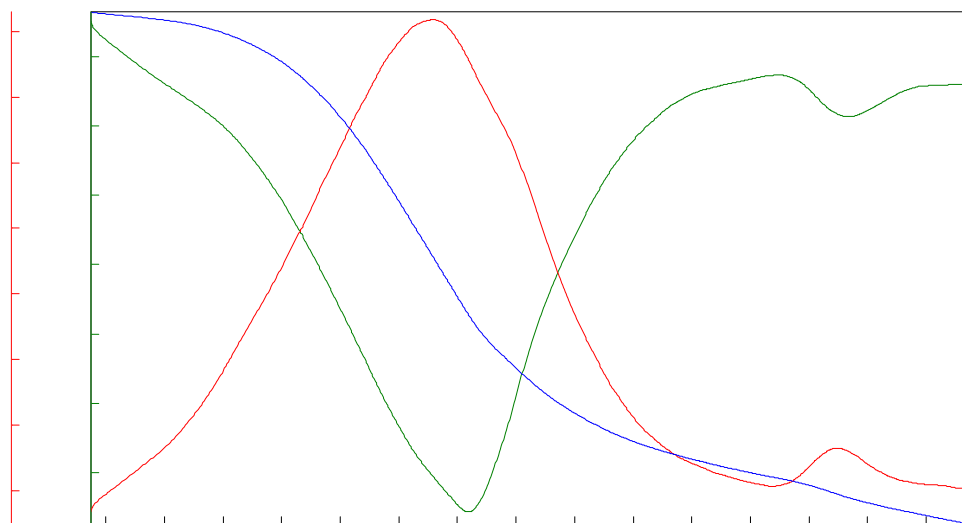


Figure 7. Thermal analysis (TG , DTA, DTG) of prodrug polymer (P2)

TG analysis of (P2) as prodrug polymer the temperature is 42 C° , and weight loss (97%), so temperature (54 C°) is matched to (91%) as a weight loss, also the temperature (68 C°) and the weight loss is (88.5%), while for DTA analysis of polymer (P2) the temperature was (36 C°) is corresponded to 93% and the temperature (89 C°) is matched weight loss 87.5% , and 89 C° is corresponded to 88% as a weight loss , and (DTG) analysis of same polymer (P2) the temperature (51 C°) is matched (87%), so temperature (70 C°) is corresponded (97.5%), while the temperature at (84 C°) for the weight loss (97%).^[21]. Differential scanning calorimetry of prodrug polymer (P1) curve show's a sharp peak at (56.5 c°) for an exothermic reaction according to the figure (6) , and for the other prodrug polymer (P2) the diagram appear's a sharp peak too at (58.8 c°) for an exothermic reaction again⁽²²⁾, as shown in the figure (7) While for ciprofloxacin prodrug polymer (P2) has a nother sharp peak of exothermic reaction at (58.8 C°) in the figure (7) due to the melting point of Ciprofloxacin polymer^(22, 23).

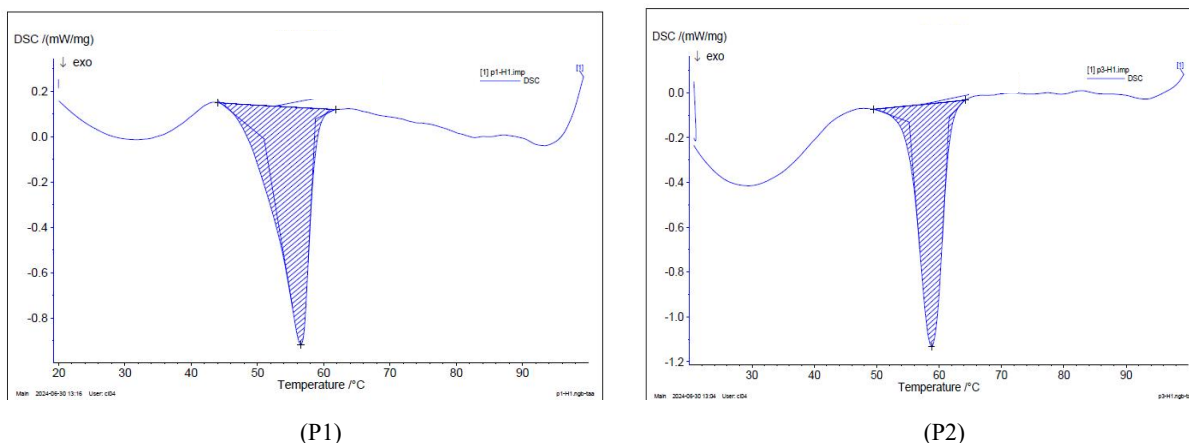


Figure 8. DSC thermograms of polymer (P1,P2)

3.4. Swelling Ratio of Polymers

The swelling term mark's to the capability of absorption large amount of water without missing it's original geometry. The differences of swelling ratio for both polymers (P1 and P2) are related to the protonation of amine group of chitosan. [24]

As shown in the table and the figure (7)

Table 2. swelling ratio of Prodrug polymers (P1, P2)

Time	%Swelling ratio P1	%Swelling ratio P2
24h	80.66666667	120.66666667
48h	178.3333333	145
72h	208.5	199

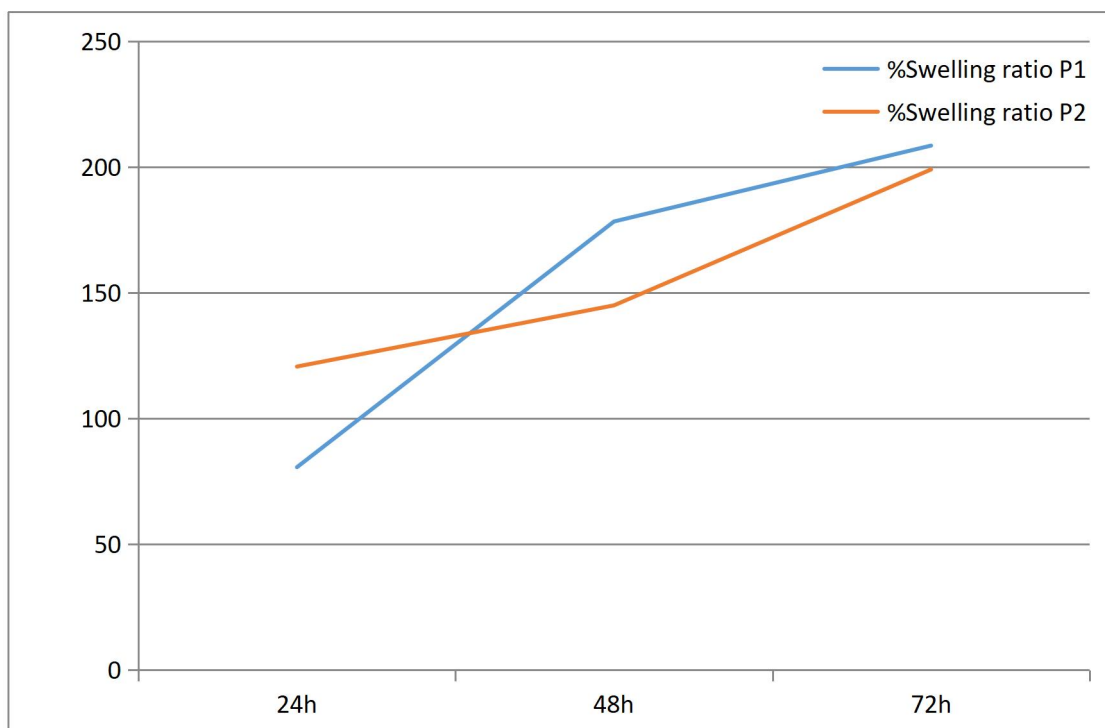


Figure 9. Swelling ratio of Prodrug polymers (P1, P2)

3.5. Controlled Drug Release of Polymers

The drug delivery system keep constant the drug level in blood and tissue for an extended period also controlled drug release maintain drug plasma levels constantly by fixed the release of drug dose at each time point for apre – determined duration in order to reduce the dose and dosing frequency and for improving the bioavailability^[24]. The release rate and mechanism in vitro are strongly influenced by structure, composition , composition ratio, and interaction between drug and polymer, so polymer swelling, absorption of drugs, degradation and drug diffusion ^[25,26].

Table 3. Controlled Drug Release of (P1 , P2) polymers

Time (hours)	P1 Abs (nm)	P2 Abs (nm)
0	0	0
1	0.009	0.062
2	0.011	0.07
6	0.013	0.087
12	0.015	0.109
24	0.017	0.119
48	0.018	0.13
72	0.018	0.135

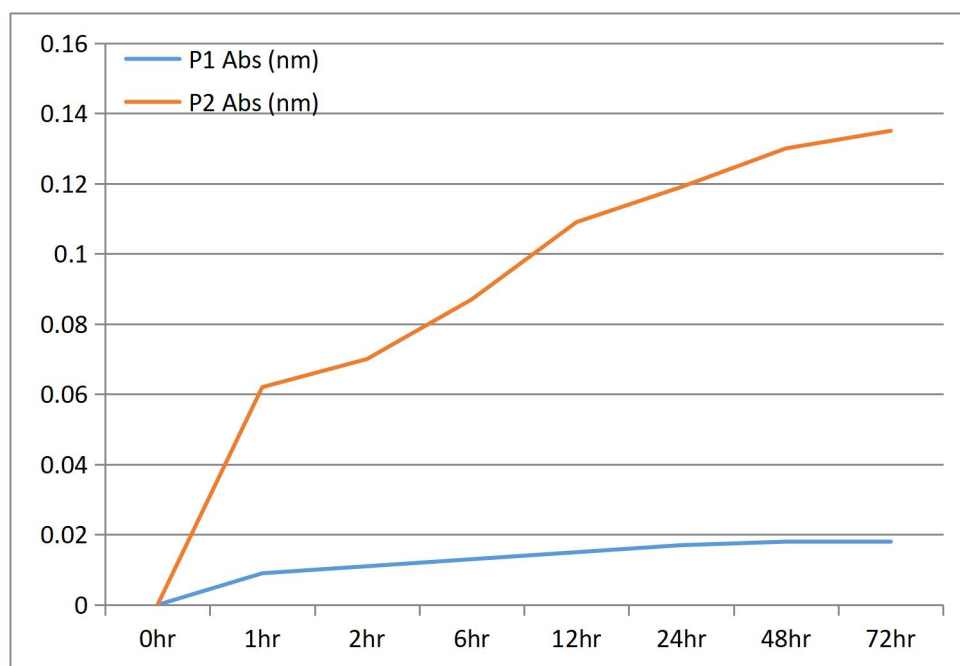


Figure 10. Controlled Drug Release of (P1 , P2) polymers

3.6. Antioxidants application of Polymers

Polymeric antioxidant scavenage a variety of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Phenolic antioxidants are commonly used as anti oxidant with many hindered with limited solubility in water and limited absorption, also polymers were used as a drug delivery vechile for delivering anti-oxidants to the target site .

Antioxidants play an important role in the polymer industry there are two types of antioxidants: 1- primary antioxidant has the ability of neutralizing some of the radicals($R\cdot$, $RO\cdot$, $ROO\cdot$, $HO\cdot$) by proton transfer, 2- secondary antioxidant type which break down by formed hydroperoxides ($ROOH$) due to the steric hinderence of phenolic group (OH), so this will reduce the ability of intermolecular hydrogen bonds to make prodrug

polymer (P₂) is highly DPPH scavenged percent than the other polymer (P₁) as an effective antioxidant polymers^(27, 28).

Table 4. Antioxidant activity of Prodrug Polymer (P₁, P₂)

Concentration (mg/ml)	DPPH Scavenging (P ₁) (%)	DPPH Scavenging (P ₂) (%)
0	0	0
0.15625	72.00902935	75.62076749
0.3125	74.71783296	77.42663657
0.625	76.9751693	78.55530474
1.25	79.00677201	80.13544018
2.5	81.26410835	82.61851016

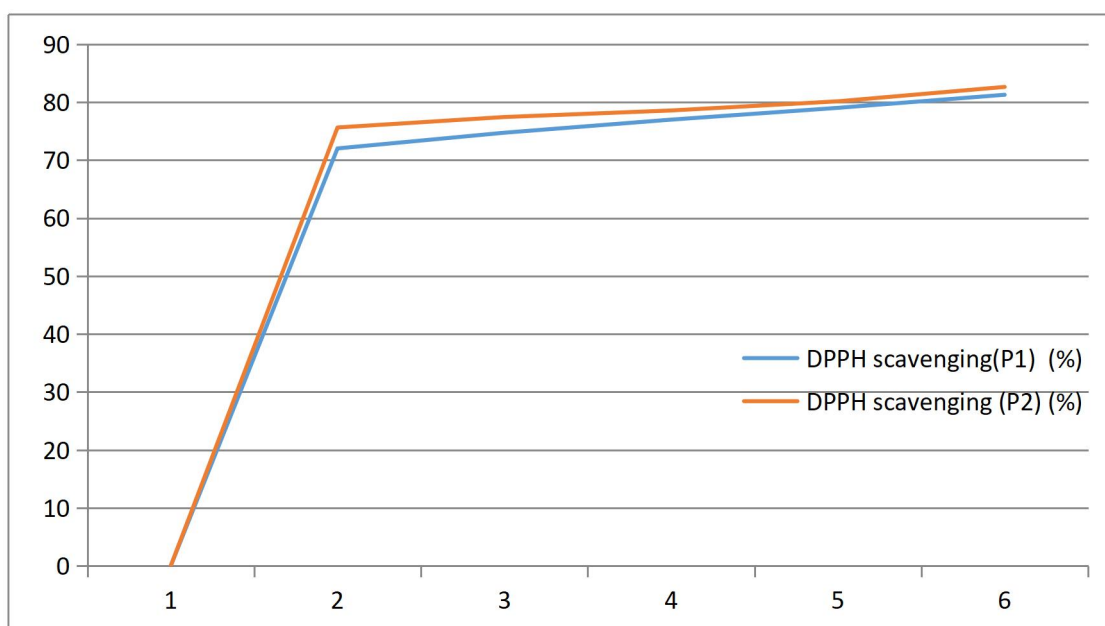


Figure 11. Antioxidant activity of Prodrug Polymers (P₁, P₂)

4. Conclusion

According to these results of the research it can be concluded that the optimum temperature of synthesizing polymer was (60 c°) and the yield color is deep green and the reaction is exothermic for both polymers (P₁ and P₂) , also these polymers have suitable values of swelling ratio and controlled drug release , lastly these polymers act an effective antioxidant polymers.

Conflict of interest

The authors declare no conflict of interest

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