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New Functional Biologically Active Polymers Based On N-Substituted Maleimides

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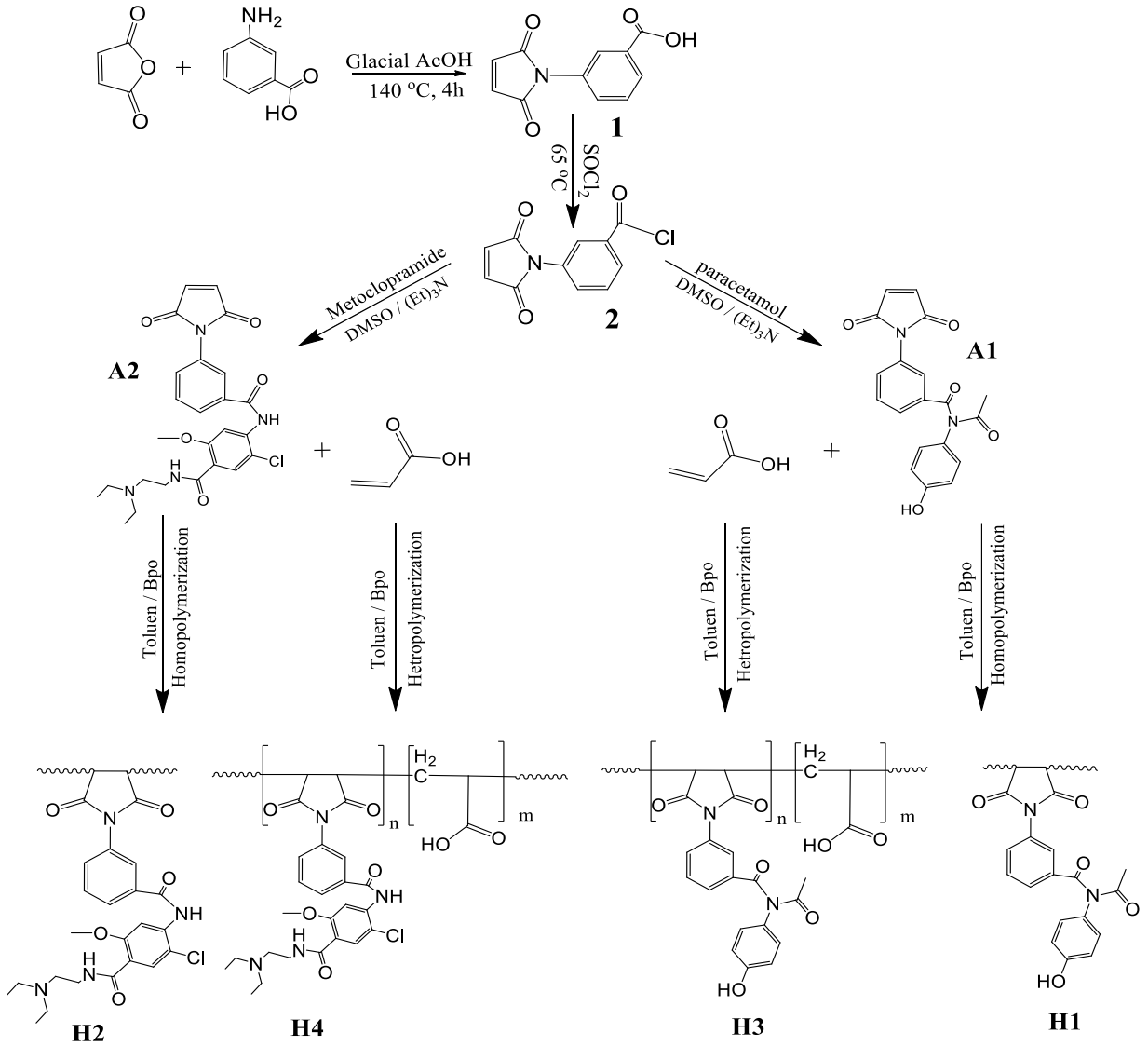
Abstract. New homogenous and heterogeneous polymers have been derived from two maleimide monomer through imidization of m-aminobenzoic acid with maleic anhydride in glacial acetic acid. The resulting 3-maleimide benzoic acid was converted to acid chloride derivative and condensed with two amino drugs (Paracetamol and Metoclopramide) respectively, in presence of triethyl amine as catalyst afforded two new maleimide-drug monomers (A1and A2). Homo-polymers (H1and H2) and Hetero-polymers (H3 and H4) were synthesized via polymerization of each of A1 and A2 with equal amount of acrylic acid, benzoylperoxid (Bpo) used as an initiator under nitrogen atmosphere. All prepared compounds were characterized by FT– IR and ^{1}H NMR, and screened for their antibacterial activity against pathogenic strains of E.coli (ATCC 8739) and S. aurous (ATCC25923) at concentration of 0.5 mg/mL using corresponding drugs as standards by disk-diffusion method. The results show increase in the antibacterial activity for monomers and polymers comparison to the Paracetamol and metoclopramide drugs control. The drug release and swilling ratios of prepared polymers were investigated.

Keywords: Metoclopramide**,** Paracetamol, antibacterial activity, Drug release.

Introduction

Maleimides and their related compounds have interesting properties, especially when they can be used as selective inhibitors for monoglyceridelipase(1), and several enzymes containing reactive cysteinyl residues(2). Maleimide derivatives improved the building blocks using in the fields like pharmaceutical chemistry, polymer chemistry, and material science. Many researches are motivated to synthesize functional polymers used in different biomedical applications like antimicrobial(3,4), water purification (5), wound dressings and protective bandages (6), antimicrobial agents(7), and anticancer (8). Current studies have reported the use of conjugated polymers with drugs acting to inhibition of specific kinases(9), apoptotic routes and angiogenesis (10).

Here we have synthesized new four polymers based on two maleimide-drug derivatives by condensation of m-maleimide benzoic acid with Paracetamol and Metoclopramide, which could be useful in a range of biological applications.



Scheme 1: Synthesis route of compounds (H1-M4)

Experimental and Methods

Both solvents and reagents were provided from Fluka, Sigma-Aldrich, CDH, and Riedel-de Haen, which were in analytical grade. Paracetamol and metoclopramide was supplied from SDI-Samarra Company. SMP30 melting point equipment was used to calculate melting points. The UV absorbance was measured using a PG CECIL- CE7200 double beam spectrophotometer. METTLER TOLEDO (Densito 30px Portable Density Meter) was used to assess the densities of polymer sample solutions at 23 ˚C. An Ostwald viscometer was used to calculate the viscosity (η) of the prepared polymers in acetone at 23 ˚C. The 1HNMR spectra were obtained in dimethyl sulfoxide (DMSO-d6) using a Varian INOVA 500 MHz NMR spectrometer; chemical changes are in units (ppm). The IR spectra were recorded using a Bruker Tensor II Fourier Trans Infrared Spector Promoter AT-FT-IR within the range (400-4000) cm-1.

Synthesis of compound [1]: N-(3-Carboxyphenyl) maleimide (m-CPMI)

A solution of m-aminobenzoic acid (6.85 g, 0.5mol) and maleic anhydride (4.9 g, 0.5 mol) in 75 mL of Glacial acetic acid was stirred continuously for 2 hrs. at room temperature until yellow precipitate of m-

maleamic benzoic acid was formed (R_f = 0.4 / 1hexane : 3ethylacetate). Then the mixture was refluxed for 4 hrs. at 140 °C until it became a homogenous light brown liquid. The solution was concentrated using rotary evaporator and then poured in ice crushed and left for two hours until a yellow precipitate was formed. The precipitate was filtered and washed with 1% aq. $NaHCO_3$ with large excess amount of distilled water then dried and then recrystallized from ethyl acetate obtaining the product in (6.5 g, 60% Yield) with mp 238-240 °C (Lit. mp. 239-241 °C)(11). Color: Yellow. FT-IR (cm^{-1}): ~ 3500-2551 (COOH), 3098 and 3003 (=C-H,maleimide and aromatic), 1709(CO-N-CO, imide), 1693(C=O, carboxylic acid), 1606-1473 (Aromatic C=C), 1378 (C-N stretching)(12), 852 and 834 (=C-H,oop).

Synthesis of compound [2]: N-[3-(Chlorocarbonyl) phenyl] maleimide (m-CPMIC)

A solution of(4.29 g, 0.011 mol) m-CPMI **1** in chloroform (30 mL) and 1.55 mL thionyl chloride was refluxed at 65 °C for 3 hrs. The solvent was evaporated under reduced pressure and dried. The residual product was recrystallized from DCM to obtain pure light yellow crystals of acid chloride, (90% Yield, mp. 125-127 °C), (Lit.mp = 126–128°C) (11). FT-IR (cm^{-1}): 3165 and 3088 (=C-H, maleimide and aromatic), 1774 (COCl), 1714, (CONCO, imide), 1601-1483 (C=C, aromatic), 1379 (C-N), 889 and 831 (=CH, oop).

General Procedure for the Synthesis of Maleimide-Drug Monomer Derivatives [A1 and A2]

(1 g, 4 mmol)of 3-maleimide benzoyl Chloride **2** was added to stirred solution of 4 mmol of two Drugs (Paracetamol and Metoclopramide) in 10 mL DMSO and 1 mL of triethylamine (TEA) at room temperature for 1 h., and then heated for 2hrs at 60 °C until the TLC reactant spot was vanished. The final solution was poured in ice crushed, left for (30min),until colored precipitate had formed, and then filtered, dried and further crystallized from acetone.

Compound [A1]: Chemical Formula: $C_{19}H_{14}N_2O_5$, color: Reddish Brown, (mp.= 111-113 °C, Yield 70%) . FTIR (cm^{-1}): 3292 (-OH, of phenol), 3080 (=C-H, aromatic rings and maleimide), 2975 (C-H, methyl), 1711 (CO-N-CO, imide), 1666 (C=O, amide), 1588-1452 (C=C, aromatic), 1376 (C-N), 1185 (C-O stretching). ^{1}HNMR (500 MHz, DMSO, δ ppm):2.065 (s, 3H, $-CH_3$), 2.487 (DMSO)[13], 3.350 (H_2O)[13], 6.657 and 6.684 (d, 2H, CH=CH), 7.206 -7.358 (m, 4H, ph- protons), 7.673-7.960 (m, 4H, benzene protons), 10.683 (s, 1H, phenol).

Compound [A2]: Chemical Formula: $C_{25}H_{27}ClN_4O_5$, color: pale red, m.p.= 122 – 124 °C, yield 75%. FTIR (cm^{-1}) 3361 and 3272 (-NH, amide groups), 3129 and 3064 (C-H, sp^2, of aromatic rings and Olefenic H-C=C-H of Maleimide), 2979-2874 (sp^3 C-H), 1714 (CO-N-CO, in an imide ring), 1628 (C=O amide of metoclopramide drug and C=C), 1590 (amide stretching) 1508-1443 (C=C, aromatic), 1396 and 1383 (C-N), 1035 (C-O, of O-CH_3), 7851, 807 (=C-H,oop), 746 (C-Cl) .

^{1}HNMR (500 MHz, DMSO, δ ppm): 1.170 (s, 6H, 2-CH3), 2.508 (s, 4H, 2N-CH2-), 2.567 (DMSO), 3.066 (H_2O), 3.592 and 3.817 (4H, $-CH_2-CH_2$), 3.918 (s, 3H, $-OCH_3$), 7.196 (s, 2H, CH=CH), 7.451- 7.969 (m, 4H, benzene protons), 8.247 and 8.549 (2H , Ar-H of drug), 10.111 and 10.343 (2H, 2-NH- Amide).

General Procedure for the Synthesis of homo-polymers [H1and H2]

Monomers A1and A2 (1 g) was mixed individually with 20 mL of toluene in a 50 mL two neck round bottom flask, which was tightly sealed and placed in an oil bath at 110 ºC and 0.05 g of Benzoyl peroxide, (Bpo) was added to the reaction mixture as initiator. The reaction mixture was refluxed for 10 hrs. under nitrogen blanket and at the end of polymerization, The precipitate was filtered, washed using diethyl ether and finally dried in an oven at 45 ºC overnight.

Compound [H_1]: color: Reddish Brown. FTIR (cm^{-1}): 3322 (-OH, phenol), 3043 (=C-H, aromatic rings), 2978 and 2945 (C-H, methyl) , 1711 (CO-N-CO, imide), 1668 (C=O, amide), 1607-1475 (C=C, aromatic), 1382 (C-N), 1035 (C-O). ^{1}HNMR (500 MHz, DMSO, δ ppm) 2.065 and 2.091 (d, polysuccinimide protons), 3.065 (s, 3H, -CH_3), 7.237-7.499 (m, 4H, ph- protons), 7.613-7.945 (m, 4H, benzene protons), 9.995 (s, 1H, phenol-OH).

Compound [H2]: color: reddish Brown. FTIR (cm^{-1}): 3363 and 3232 (-NH, amide), 3004 (=C-H, aromatic), 2978-2737 (C-H, methyl and methene), 1712 (CO-N-CO, imide), 1627 (C=O amide), 1590-1475 (C=C, aromatic), 1381 (C-N), 1035 (C-O), 744 (C-Cl stretching). ^{1}HNMR (500 MHz, DMSO, δ ppm): 1.193 (s, 6H, 2-CH_3), 2.074 (s, polysuccinimide protons), 2.493 (DMSO), 3.072 (s, 4H, 2N-CH_2-) and (H_2O), 3.605 and 3.822 (4H, -CH_2-CH_2-), 3.938 (s, 3H, -OCH_3), 7.491- 7.968 (m, 4H, benzene protons), 8.358 and 8.647 (2H , Ar-H of drug), 10.153 and 10.409 (2H, 2-NH- Amide).

General Procedure for the Synthesis of hetero polymers [H3 and H4]

In a dry two neck round bottom flask , (1.77 mmol), from each prepared monomer and acrylic acid in 25 mL of dry toluene and (0.01 g) of the initiator Benzoyl peroxide (Bpo) was added with flushing nitrogen gas for (10 mins), the flask was tightly sealed and refluxed on oil bath at 110 °C for 6 hrs. The precipitate was filtered, washed with ether and dried in oven at 50 °C.

Compound [H3]: Color Reddish Brown. FTIR (cm^{-1}): ~3500-2530(COOH), 3303 (-OH, phenol), 3076 (=C-H, aromatic rings), 2978 and 2882 (C-H, aliphatic), 1718 (CO-N-CO, imide and C=O of acrylic acid), 1604 (C=O amide), 1545-1396 (C=C, aromatic), 1329 (C-N), 1034 (C-OH).
^{1}HNMR (500 MHz, DMSO, δ ppm): 1.973-2.652 (polysuccinimide-Co-acrylic acid backbone protons), 2.493 (DMSO), 3.065 (s, 3H, -CH_3), 3.331 (H_2O), 7.231-7.636 (m, 4H, ph- protons), 7.766-7.997 (m, 4H, benzene protons), 10.135 (s, 1H, phenol-OH), 12.634 (s, 1H, COOH).

Compound [H4]: color, reddish Brown. FTIR (cm^{-1}): the broad band within the range from 3467- 2531 (COOH), 3364 (-NH, amide groups), 3066 (=C-H, aromatic rings), 2979 and 2963 (C-H, aliphatic), 1711 (CO-N-CO, imide ring and C=O of acrylic acid), 1627 (C=O, amide), 1586-1449 (C=C, aromatic), 1382 (C-N stretching), 1037 (C-O, of ether), 750 (C-Cl) .

^{1}HNMR (500 MHz, DMSO, δ ppm): 1.182 (s, 6H, 2-CH_3), 1.894, 2.002, 2.078 and 2.628 (polysuccinimide-Co-acrylic acid backbone protons), 3.038 (s, 4H, 2N-CH_2-), 3.589 (4H, -CH_2-CH_2-), 3.837 (d, 2H, -CH_2-N-CO-), 4.226 (s, 3H, -OCH_3), 7.248- 7.960 (m, 4H, benzene protons), 8.306 and 8.608 (2H , Ar-H of drug), 10.140 and 10.349 (2H, 2-NH- Amide).

Results and discussion

Spectroscopic analysis

Synthesis of the titled maleimide compounds (A1 and A2) has been depicted in scheme 1. The intermediate 3-Maleimido benzoyl chloride **2** was obtained by refluxing of 3-maleimidobenzoic acid in thionyl chloride at 70 ^oC for 1 h, the excess of $SOCl_2$ was drawing under reduce pressure, then recrystallized from dichloromethane. The structure of compound **2** was confirmed by FT-IR spectrum which shows disappearing of the broad absorption of carboxylic acid and appearance of strong band at higher frequency, 1769 cm^{-1}, that is absolutely belongs to (COCl) group.

Equimolar amounts from 3-Maleimido benzoyl chloride **2** and two standard drugs (Paracetamol and metoclopramide) separately dissolved in DMSO and 1.1 equivalent of triethylamine were used to produce two maleimide monomer derivatives. FT-IR spectrum of the synthesized compounds (A1and A2) shows strong stretching frequencies for the Maleimide carbonyl groups at 1711–1714 cm^{-1} and disappearance of (-COCl). The ^{1}HNMR spectra for maleimide compounds shows characteristic signals for maleimide (CH=CH) protons at 6.657 and 6.684 ppm for A1 (CH=CH) protons and 7.196 ppm A2 compound.

The disappearance of these proton signals from co-and homopolymers^{1}HNMR spectra as well as the broad and weak signals of acrylic acid hydroxyl protons of copolymer spectra gives strong evidence for the success of the polymerization reaction. The physical properties of monomers listed in Table 1.

Table 1: Physical properties of prepared monomers [1, 2, A1and A2]

Comp.	Color	Yield (%)	m.p. °C	Rf
1	Yellow	60%	238-240 °C	0.4 1hexane:3ethylacetate
2	Light Yellow	90%	126-128 °C	0.75 1hexane:3ethylacetate
A1	Reddish Brown	70 %	111 – 113 °C	0.85 1hexane : 3acetone

A2	pale red	75%	122 – 124 °C	0.80 1hexane : 3acetone

The prepared monomers were polymerized in toluene at 110°C for 10 hrs under nitrogen flow with traces of benzoylperoxid as an initiator to yield [H1-H4] Hetero and homopolymers with the following physical properties listed in (Table 2):

Table 2: physical properties of Co- and Homopolymers [H1-H4]

polymer	color	T °C	$t_{S\ D.W}$	$t_{unk}S$	d_{unk}	$d_{D.W}$	$\eta_{D.w}$ poise	η_{unk} poise
H1	Orange	23	131.39	119.5	0.792	0.990	0.960	0.699
H2	Red			114.7	0.788			0.667
H3	yellow			115.2	0.793			0.675
H4	Brown			115.1	0.786			0.668

Solubility: The synthesized monomers and polymers were insoluble in water and acidic media, while it soluble in basic aqueous solution (pH=7.5-8). Solubility properties of prepared polymers in different solvents (H_2O, ethanol, $CHCl_3$, ether, toluene, DMSO, hexane, DMF and acetone) are listed in (Table 3).

Table 3: The solubility of synthesized Homo-polymers

sample	H_2O	EtOH	$CHCl_3$	Ether	Toluene	DMSO	Hexane	DMF	Acetone
H1	-	+	partial	-	partial	+	-	+	+
H2	-	+	partial	-	partial	+	-	+	+
H3	-	+	-	-	partial	+	-	+	+
H4	-	+	-	-	partial	+	-	+	+

Swelling ratio: dissolving 0.05 g of homopolymersxerogel in 50 mL distilled water, the swelling ratio was determined. It was left to soak for various amounts of time (25 ˚C) for 1 hour - 24 hours, the hydrogel was separated from the bath, blotted with filter paper to extract surface water, measured, and the swelling ratio was calculated using the equation below.

$$\text{Swelling ratio (\%)} = \frac{\text{wt.of hydrogel wt.of xerogel}}{\text{wt.of hydrogel}} \times 100$$

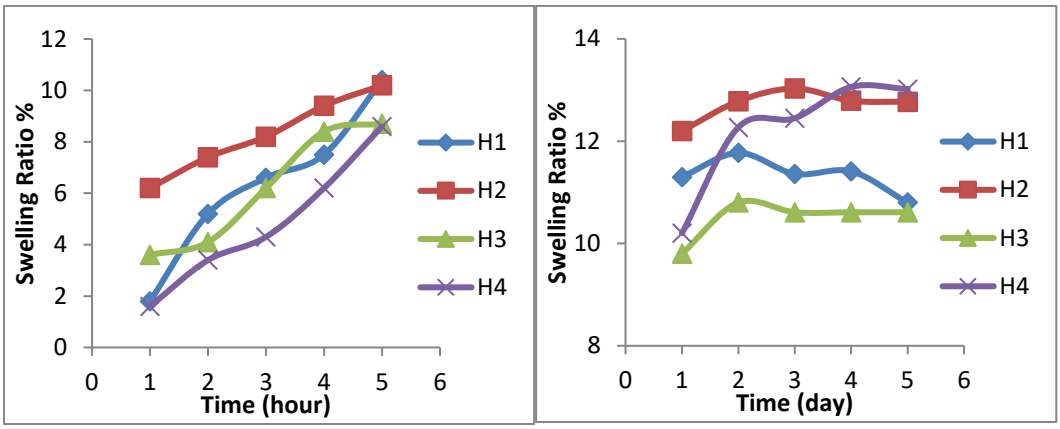


Figure 15: The Swelling diagrams of prepared polymers[H1-H4]

The Antibacterial Activity of Monomers and Homopolymers

The anti-bacterial activity for all synthesized compounds and their loaded drugs are listed in (Table 5):

Table 5: Antibacterial activity of compound A1, A2, H1-H4 at 0.5 mg/mL concentration

Inhibition zone (mm) for tested microorganisms		
Samples	S. aurous	E. coli
Monomer		
A1	16	15
A2	18	14
H1	20	22
H2	16	20
H3	10	25
H4	25	24
Drug		
Paracetamol	8	6
Metoclopramide	9	10

The disk-diffusion approach was used to test antibacterial activity(14-16) against pathogenic E. coli and S. aureus strains using a solution of 0.5 mg of each compound and each loaded drug for contrast in 1 mL of DMSO. In addition, the activity of DMSO was tested as a negative control, which showed no inhibition of bacterial development.

The results according to table 3 shows that A1 and A2 monomers have moderate inhibition zone (16 and 18 mm) against S. aureusand (15 and 14 mm) against E. coli in comparison to Paracetemol and Metoclopramide drugs, inhibition. While, good inhibition of growth for homopolymers (H1 and H2) as well as Heteropolymer (H3 and H4) against both bacteria with higher effect toward E. coli. The lipophilic and neutral nature of maleimide enables it to move across biological membranes with ease (17-19). The cell

walls of Gram negative bacteria are made up of one or more layers of peptidoglycan and a lipid-rich outer membrane (20-34), which may explain why they have better antibacterial action against E. coli.

Release of drug: Drug release from the prepared polymers was measured in two separate buffer solutions (pH= 2 and 8.0) at 24°C using a UV-visible spectrophotometer. Figures 16 and 17 show the drug release from the polymers.

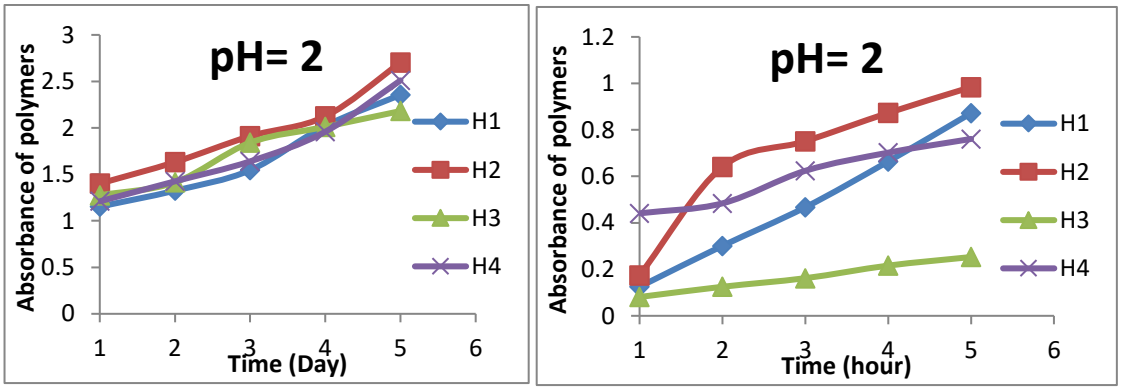


Figure 16: The Drug release diagram of Co- and Homopolymers (H1-H4) at PH= 8.

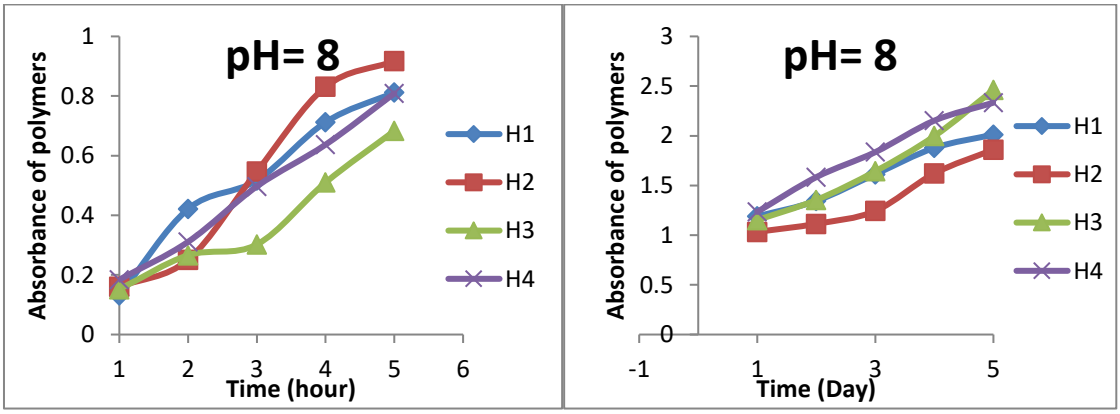


Figure 17: The drug release diagram of Co- and Homopolymers (H1-H4) at PH= 8

Conclusion

New Prodrug polymers based on maleimide-drug monomers were successfully prepared via a free radical polymerization reaction. Their structures have been confirmed using FTIR and ^{1}HNMR techniques. Most of synthesized compounds, having a high antimicrobial activity as proved by their higher inhibition zone diameters. All polymers show a good drug release in the basic medium. Based on antimicrobial activity, the prepared polymers could be an acceptable and promising strategy for developing effective drugs to biological application

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