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Synthesis and application of some Drug-conjugated Poly *p*-styrene sulphonate for drug release Delivery

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Abstract
Controlled drug release is one of the most important methods to increase the therapeutic effects and decrease side effects of drug. In this research, three drugs (piperazine, 8-aminoquinoline, N-phenyl piperazine) were attached chemically to the p-styrene sulphonyl chloride (as monomer), and they were polymerized by AIBN (Azobis isobutyro nitrile) at 80 °C. Finally, release ability of three polymer-drugs were tested in buffer solution with pH= 1.3 at the temperature 37 °C. The GPC spectra of the polymers showed that polymerization of monomers containing drugs were carried out. The results established that, these polymeric systems are able to release drugs.

Keywords*:* drug, p-styrene sulphonylchloride monomer, polymerization, drug delivery.

1. Introduction

For more than three decades, the delivery of bioactive agents from polymeric materials has attracted considerable attention. It has proved that controlled release is useful in some areas such as foods, cosmetics, and pesticides, [1] but the largest impact is in the field of drug delivery [2].

Polymer-based delivery systems enable to control slow release of drugs into the body. Drug delivery research is substantially focused on improving methods to deliver medications to the necessary location, in the correct amount, at the correct time [3].

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. Since some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels. The goal of designing sustained and controlled release drug delivery systems is reducing the frequency of the dosing or increasing effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery [4]. So, the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials that are suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety that achieved by these delivery systems. Improved drug safety could be often achieved by controlling the rate of drug delivery through dosage form [5].

In order to successfully usage drug in such drug delivery system, the administration route plays a vital role, the choice of a delivery route depends on some factors such as: patient acceptability, properties of the drug (such as its solubility), access ability to the treatment site, effectiveness in dealing with a specific disease [6]. Polymers have been used as a main tool to control the drug release rate through the formulations. Extensive applications of polymers have been realized in drug delivery because polymers offer unique properties which have not been attained by any other materials.

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Polymers are macromolecules having very large chains, and contain a variety of functional groups. They can be blended with other low- and high - molecular-weight materials, and can be used for any applications. Polymers are increasingly getting importance in the field of drug delivery. Advances in polymer science have led to the development of several novel drug-delivery systems [7].

Chemical drug delivery systems (CDSs) are defined as chemical compounds that are produced by synthetic chemical reactions forming covalent bonds between the drug and specifically designed "carrier" and other moieties. At least one chemical bond needs to be broken for release of active component (drug) [8]. Synthetic polymers which used in biomedical applications are making a significant contribution to the progress in health care. In constructing a drug delivery system from organic materials, targeting molecules, and drugs are restricted to ensure stability, inexpensive, chemical inertness, biocompatibility and minimum undesirable degradation byproducts, non-leach ability, ease of fabrication and sterilization, [9] and simple constructing of carrier polymer.

The best way of choosing an appropriate polymeric support involves defining, with respect to the nature of the reactive functional group used to link the molecule, the chemical nature of the linking used bond, and in particular whether it must be stable or not towards hydrolysis. One can then choose, between the structures of the known polymers, the one which facilitates the chemistry requires [10]. This restriction can be reduced by using the monomer (p-styrene sulphonyl chloride) and polymerization of the monomer-drug. Being of double bond in the monomer backbone for polymerization, and the ability of hydrolysis of drug-polymer bond in body buffer medium is most important advantages of this system. In this research, mechanism of releasing drug within the body occurs through hydrolytic cleavage of S-N bond. This system is called "chemically controlled release system" in which drug is chemically bonded to the polymer carrier backbone as chain [11]. The kinetic studies related to hydrolysis of arylsulphonates were investigated in some reviews [12-14].

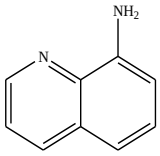
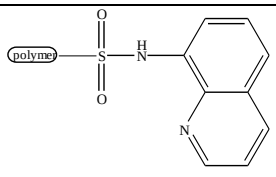
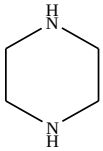
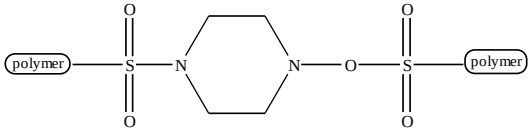
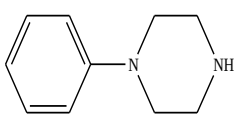
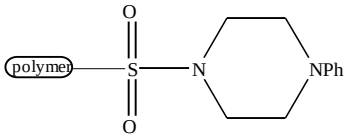
The objectives of present research are: (1) reaction of three drugs with p-styrene sulphonyl chloride (as monomer), (2) polymerization of the obtained drug-monomers by AIBN as an initiator (3) the release mechanism study of three drugs from poly (p-styrene sulphonyl) as chemically controlled release system, (4) elaborate the spectra and GPC chromathograms of drug-polymers, (5) hydrolysis of three drug-polymers in phosphate buffer with pH=1.3 at 37°C temperature, and (6) specification of the percentages and amounts (ppm) of hydrolyzed drugs from their polymers. Table 1 shows the structures and properties of the three drugs.

2. EXPERIMENTAL

2.1. Chemicals

8-Aminoquinoline, piperazine, and *N*-phenylpiperazine, PCl_5, 2,2-azobisisobutyronitrile (AIBN), triethylamine (TEA), diethyl ether, potassium chloride, hydrochloric acid, sodium hydroxide, chloroform, tetrahydrofuran (THF), and

Table 1: The structure and biological of the drugs and the potential structure of grafted polymer-conjugated Drug

Entry	Drug scaffold	Drug name (properties)	Product
1	8-aminoquinoline 	Antimalaria	
2	Piperazine 	Anthelmintic	
3	*N*-phenylpiperazine 	Antibacterial	

magnesium sulfate were purchased from Merck company, and vinylbenzenesulfonic acid sodium salt was obtained from Fluka company. All available chemical reagents were used without further purification.

2.2. Apparatus

FTIR Spectrum was taken on a Shimadzu spectrophotometer. ^{1}H-NMR Spectrum was recorded on a JEOL FT-NMR 90 MHz spectrophotometer in $CDCl_3$, DMSO-d_6 with TMS or TSP as an internal standard. Ultraviolet spectra were taken on a Shimadzu UV-265 spectrophotometer. Gel permeation chromatography (GPC) analysis was carried out on Alliance Waters GPC-2000 equipped with a refractive index detector, TCB as an eluent, and calibrated with polystyrene standards.

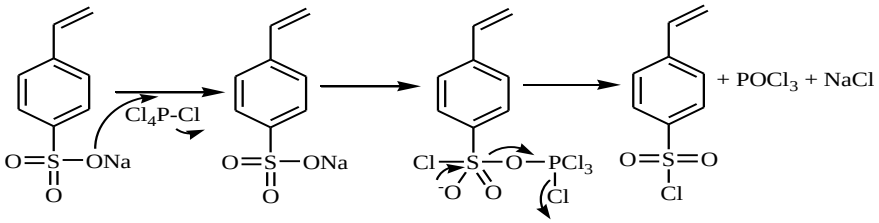
2.3. General Method

2.3.1. p-Styrene Sulphonyl Chloride Synthesis

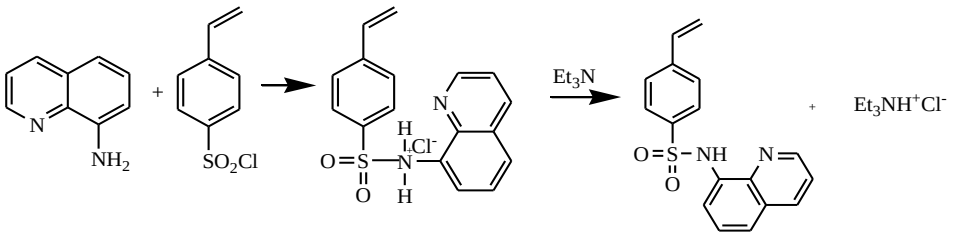
p-Styrene sulphonyl chloride monomer was synthesized by reaction of 4-vinyl benzenesulfonic acid sodium salt (5 g, 0.024 mol) with PCl5 (7.5 g, 0.036 mol) in three-necked flask equipped with magnetic stirrer, reflux condenser, and thermometer. The reaction mixture was stirred in ice water bath for a half hour until oily product was obtained. Then, the temperature was risen up to 60–70 °C. After 15 h stirring, the crude product was dissolved in chloroform and ice water, and filtered off to remove unreacted materials. Finally, the chloroform was evaporated from the *p-styrene* sulphonyl chloride. After extracting with $CHCl_3$/water and removing of organic phase, it was dried over anhydrous Na_2SO_4 (1g) (Scheme I).

2.3.2. General procedure for preparation of monomer-drug

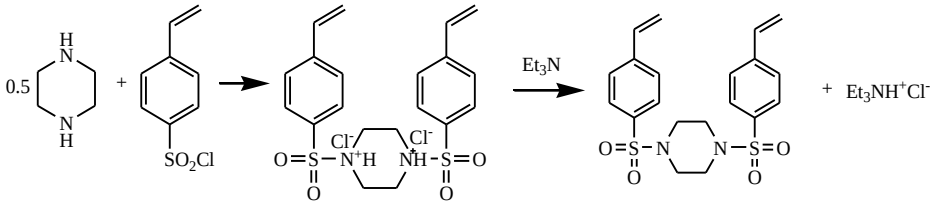
A mixture of 0.01 mol of p-styrene sulfonyl chloride, specific amount of drug (0.01mol for 8-aminoquinoline, or *N*-phenylpiperazine, and 0.005 mol for piperazine), 15 ml triethylamine and 50 ml of twice-distilled THF were placed in a three-necked flask equipped with a reflux condenser, dropping funnel, thermometer and a magnetic stirrer. After 12 h stirring at 0 °C the precipitated drug-monomer was filtered off, solvents evaporated in vacuum and the oily residue was dissolved in 50 ml of THF. The second part of separated product was removed by filtration and purified by crystallization from mixture of 50/50 hexane/chloroform. The product was filtered off and dried with 1g $MgSO_4$ (Scheme II- IV). The drug-monomers were characterized by IR and ^{1}H-NMR spectra.



Scheme I. Mechanism of *p*-styrene sulphonyl chloride synthesis



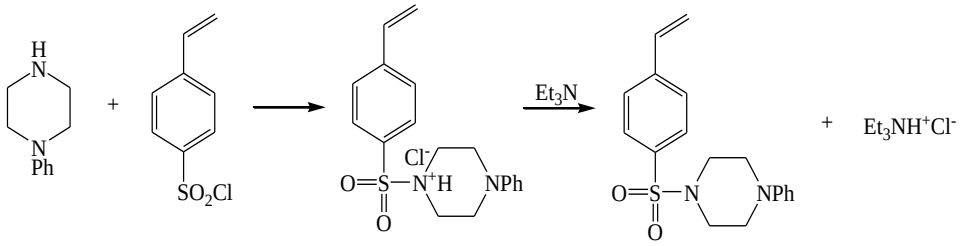
Scheme II. Mechanism of 8-aminoquinoline-*p*-styrene sulphonate monomer synthesis



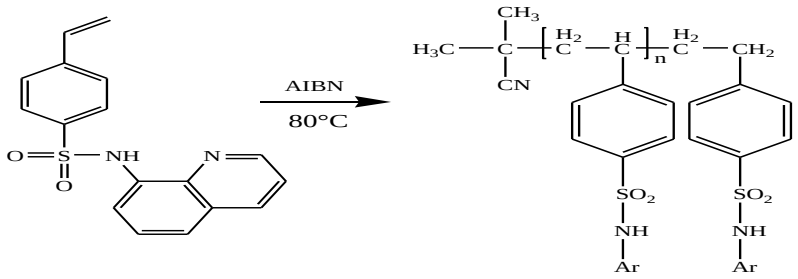
Scheme III. Mechanism of piperazine-*p*-styrene sulphonate monomer synthesis

2.3.3. Polymer Synthesis

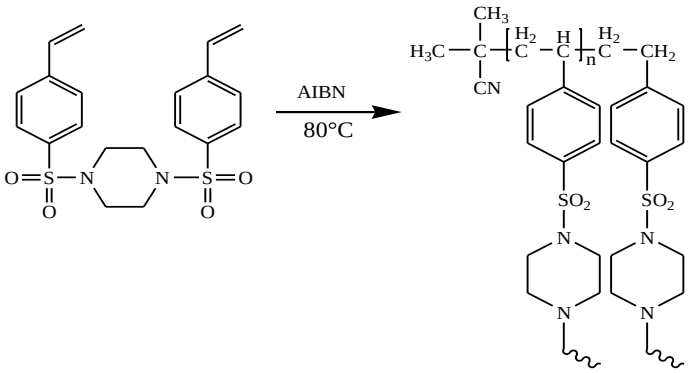
A mixture of the monomer-drug (0.1 mol), THF (50 ml), and AIBN (0.05 g) as an initiator were placed in a three necked flask equipped with a reflux condenser and a magnetic stirrer under reflux condition at atmosphere of nitrogen at 80 °C for 24 h. The polymer was purified by using a solvent system of chloroform/hexane and dried with Na_2SO_4 (1g). The solvents were evaporated under reduced pressure (Scheme V-VII).



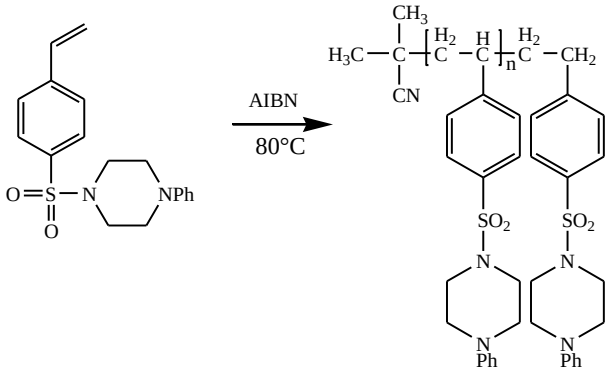
Scheme IV. Mechanism of *N*-phenyl piperazine-*p*-styrene sulphonate monomer synthesis



Scheme V. Mechanism of poly (8-aminoquinoline-*p*-styrene sulphonate) synthesis



Scheme VI. Mechanism of poly (piperazine-*p*-styrene sulphonate) synthesis

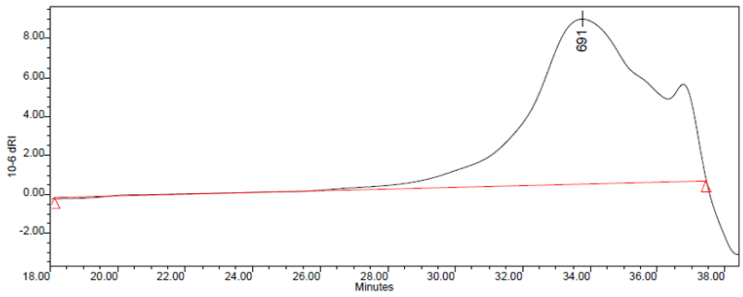


Scheme VII. Mechanism of poly (*N*-phenyl piperazine-*p*-styrene sulphonate) synthesis

The product was characterized by IR and ^{1}H-NMR spectra and GPC (Figures 1-3).

2.3.4. Controlled Release Study of polymer containing drug

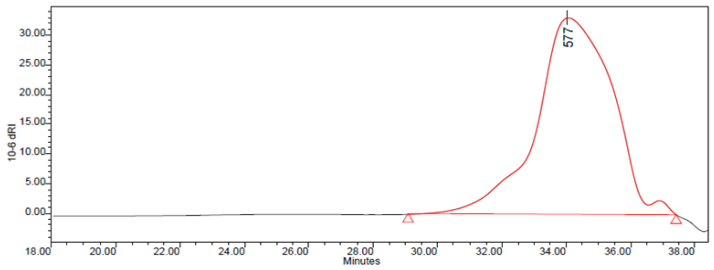
In fact drug release is a hydrolysis reaction which involves the break of S-N bond in a buffer medium. For this purpose, an amount of 0.5 g of polymer was transferred into the 7 test tubes and then 25 ml of buffer solution with pH=1.3 was added to each test tube. The test tubes were sealed with parafilm and put in a water bath at 37 °C. In specified times intervals according to the Tables (2-4), the test tubes were withdrawn from the water bath and 2 ml solution was taken from each tube. The UV spectrum of each sample was recorded after filtration. Buffer solution was withdrawn from the flask after each analysis and replaced by fresh buffer. The quantity of hydrolyzed drug (ppm) was analyzed by means of a UV spectrophotometer and was determined from the calibration curve obtained previously under the same conditions (Tables 2, 3 and 4). The absorbance of 8-aminoquinoline was measured at λ= 268 nm, piperazine at λ= 210 nm and *N*-phenylpiperazine at λ= 238 nm. In Figures 4, 5 and 6 concentration and percentage of released drugs as a function of time are shown. Schemes (VIII-X) depict these reactions.



GPC Results

	Dist Name	Mn	Mw	MP	Mz	Mz+1	Mv	Polydispersity	MW Marker 1	MW Marker 2
1		625	8364	691	801806	1330960		13.377833		

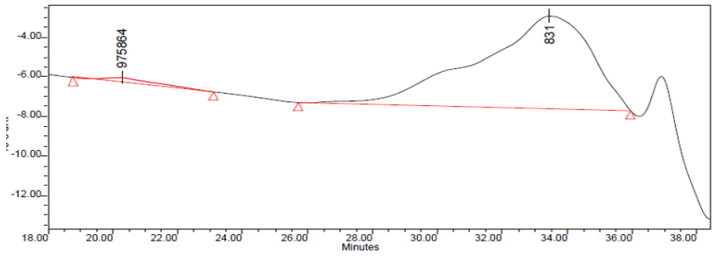
Figure1. GPC chromatogram of 8-aminoquinoline-polymer



GPC Results

	Dist Name	Mn	Mw	MP	Mz	Mz+1	Mv	Polydispersity	MW Marker 1	MW Marker 2
1		487	724	577	1216	2037		1.488641		

Figure 2. GPC chromatogram of piperazine-polymer



GPC Results

	Dist Name	Mn	Mw	MP	Mz	Mz+1	Mv	Polydispersity	MW Marker 1	MW Marker 2
1		531410	792647	975864	1099869	1401947		1.491592		
2		874	2084	831	5190	9768		2.383370		

Figure 3**.** GPC chromatogram of *N*-phenylpiperazine-polymer

Table 2: Data related to polymer containing of 8-aminoquinoline

Sample	Time (h)	Concentration (ppm)	Absorption	Released 8-aminoquinoline (%)
1	0	0	0	0
2	8	1.59	0.538	2.32
3	16	2.53	0.589	2.62
4	24	2.57	0.597	3.67
5	42	2.65	0.615	3.51
6	48	3.056	0.706	4.68
7	63	3.61	0.831	5.72

Table 3: Data related to polymer containing of piperazine

Sample	Time (h)	Concentration (ppm)	Absorption	Released piperazine (%)
1	0	0	0	0
2	8	2.020	0.261	0.661
3	18	2.264	0.312	0.752
4	24	2.451	0.318	0.817
5	42	2.901	0.476	0.967
6	48	3.051	0.644	1.016
7	63	4.814	0.726	1.604
8	72	5.058	0.817	1.686

Table 4: Data related to polymer containing of *N*-phenylpiperazine

Sample	Time (h)	Concentration (ppm)	Absorption	Released *N*-phenylpiperazine (%)
1	0	0	0	0
2	4	6.404	0.612	3.33
3	6	6.902	0.657	8.67
4	16	8.17	0.772	11.02
5	24	8.28	0.782	12.07
6	36	8.42	0.795	14.22
7	42	8.78	0.827	15.25
8	48	10.17	0.953	15.23
9	65	10.22	0.957	18.50

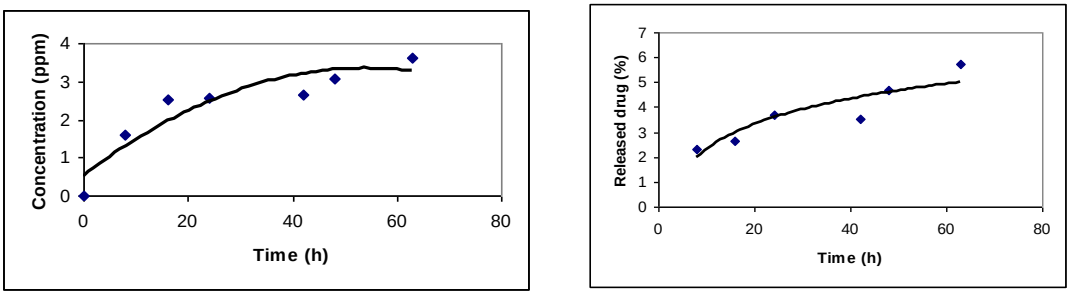


Figure. 4: Concentration and percentage of released 8-aminoquinoline

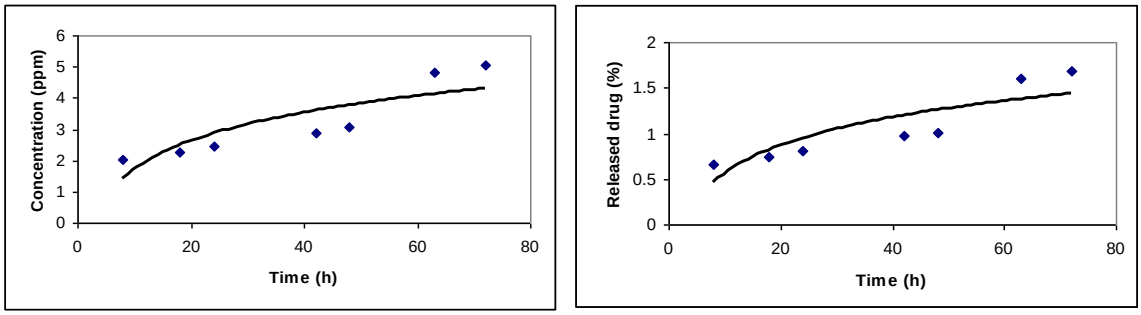


Figure. 5: Concentration and percentage of released piperazine

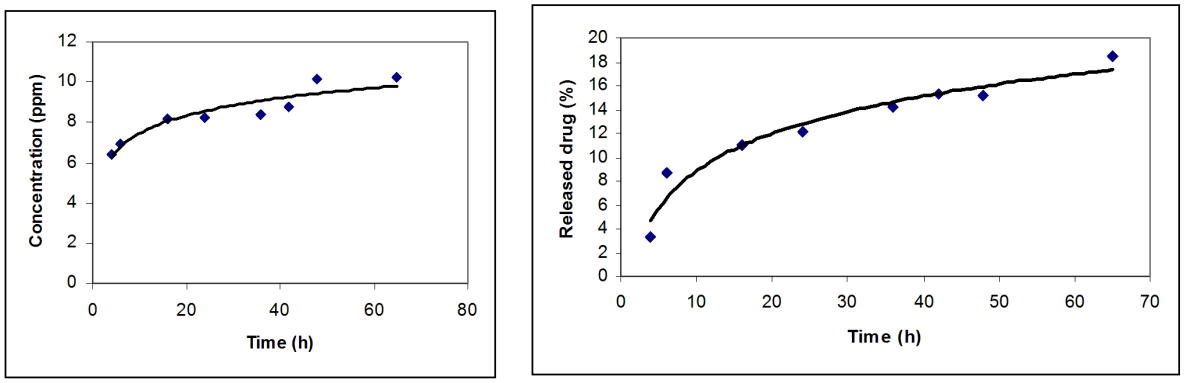
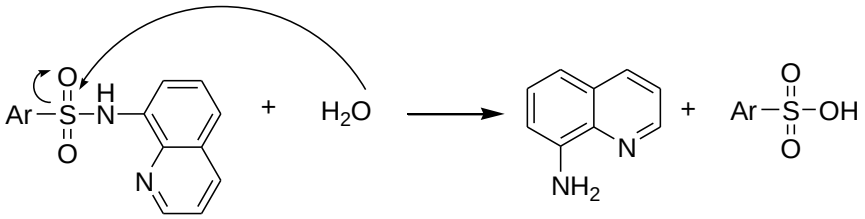
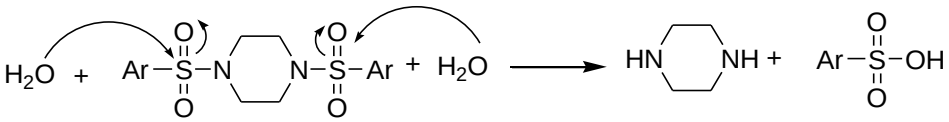


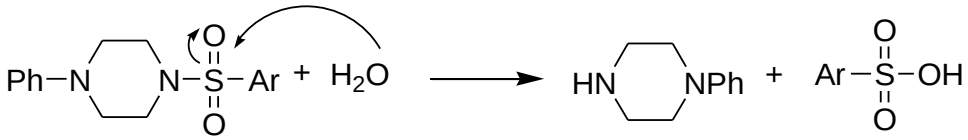
Figure. 6: Concentration and percentage of released *N*-phenylpiperazine



Scheme VIII. Mechanism of polymer-8-aminoquinoline hydrolysis in buffer



Scheme IX. Mechanism of polymer-piperazine hydrolysis in buffer



Scheme X. Mechanism of polymer-*N*-phenylpiperazine hydrolysis in buffer

3. RESULTS AND DISCUSSION

The IR and ^{1}H-NMR spectra and GPC chromatograms of the three polymers shown that the polymers are containing drugs (Figures 1-3).

The ^{1}H-NMR and FT IR spectra of monomer-8-aminoquinoline are as following: ^{1}H-NMR (90 MHz, $CDCl_3$): δ= 5.2- 6.9 ppm (s, 3H, CH_2=CH), and 7.3- 8.0 ppm (m, 10H, aromatic hydrogen), IR (KBr): 1375 cm^{-1} (asymmetric, SO_2), 1172 cm^{-1} (symmetric, SO_2), the doublet pick of –NH_2 (of 8-aminoquinoline drug) has disappeared and instead the singlet pick of sulfonamide –NH has appeared at 3296 cm^{-1} region; The ^{1}H-NMR and FT IR spectra of polymer 8-aminoquinoline are as following: ^{1}H-NMR (90 MHz, DMSO): δ= 1.7- 3.5 ppm (m, 3H-CH_2-CH-), δ = 7.6 - 9.0 ppm (m, 10 H, aromatic

hydrogen). IR (KBr): 1370 cm^{-1} (asymmetric, SO_2), 1165 cm^{-1} (symmetric, SO_2).

The ^{1}H-NMR and FT IR spectra of monomer-piperazine are as following: ^{1}H-NMR (90 MHz, $CDCl_3$): δ= 5.3- 6.9 ppm (s, 3H, CH_2=CH), and 7.3-8.0 ppm (m, 10 H, aromatic hydrogen). IR (KBr): 1372 cm^{-1} (asymmetric, SO_2), 1166 cm^{-1} (symmetric, SO_2), two picks of –NH (of piperazine drug) have disappeared at 3402 cm^{-1} region, that indicates piperazine has attached to monomer from two sides; The ^{1}H-NMR and FT IR spectra of polymer-piperazine are as following: ^{1}H-NMR (90 MHz, DMSO): δ= 1.2- 3.6 ppm (m, 3H-CH_2-CH-), δ = 7.4- 8.1 ppm (m, 10 H, aromatic hydrogen). IR (KBr): 1307 cm^{-1} (asymmetric, SO_2), 1164 cm^{-1} (symmetric, SO_2).

The ^{1}H-NMR and FT IR spectra of monomer-piperazine are as following: ^{1}H-NMR (90 MHz, $CDCl_3$): δ= 5.0- 5.9 ppm (s, 3H, CH_2=CH), the picks about 7.5 ppm (m, 10 H, aromatic hydrogens). IR (KBr): 1357 cm^{-1} (asymmetric, SO_2), 1166 cm^{-1} (symmetric, SO_2), the pick of –NHs (of N-phenylpiperazine drug) has disappeared at 3433 cm^{-1} region. The ^{1}H-NMR and FT IR spectra of polymer-piperazine are as following: ^{1}H-NMR (90 MHz, DMSO): δ= 1.1- 4.1 ppm (m, 3H-CH_2-CH-), δ = 6.9- 7.7 ppm (m, 10 H, aromatic hydrogen). IR (KBr): 1379 cm^{-1} (asymmetric, SO_2), 1164 cm^{-1} (symmetric, SO_2).

One of the most important factors in attribution of controlled release property of polymer is molecular weight. Generally, the behavior of external materials after their injection into the body is influenced by their physicochemical properties. In comparison with low molecular weight materials, polymer assemblies with high molecular weights that hardly penetrate blood vessel walls will be placed in a vascular space after intravenous injection.[15] Also, it should be mentioned that used polymers for drug delivery are biodegradable, and degradation of low weight synthesized polymers in body by microorganisms and exclusion those from body take place easily. The amounts of Mw and Mn for three polymers are shown in Table 7.

It is important to note that the amount of released drug from the polymer was obtained by comparison of calibration curves. Using the calibration curve and utilizing the amount of absorption, the concentration of released bioactive is determined. Schemes (VIII-X) indicate that mechanisms of hydrolysis of S-N bond of synthesized polymers in buffer media. The synthesized compounds can be used as controlled drug delivery systems for medicinal applications.

4. CONCLUSION

In these systems the functional group of the drug, is covalently attached to the backbone of polymer. *p*-Styrene sulphonyl (8-aminoquinoline), *p*-styrene sulphonyl (piperazine), and *p*-styrene sulphonyl (*N*-phenylpiperazine) were synthesized from reaction between p-styrene sulphonyl chloride and 8-aminoquinoline, piperazine, and *N*-phenylpiperazine respectively.

These polymers were polymerized with AIBN. The average molecular weight of obtained polymers containing 8-aminoquinoline, piperazine and *N*-phenylpiperazine drugs were 8364, 724 and 2084 respectively. The hydrolysis of drug-polymers were carried out at pH= 1.3. The effect of temperature on drug release was completely investigated.

5. ACKNOWLEDGEMENT

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سنتز و کاربرد تعدادی پلی پارا استایرن سولفونات مزدوج شده با دارو جهت آزاد سازی داروها

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چکیده:

آزاد سازی کنترل شده دارو یکی از مهم ترین روشها برای افزایش اثرات درمانی و کاهش اثرات جانبی دارو هاست. در این تحقیق، ۳ دارو (پی پیرازین ۸- آمینو کینولین و *N*- فنیل پی پیرازین) بطور شیمیایی به پارا استایرن سولفونیل کلرید متصل شده و توسط AIBN در دمای ۸۰ درجه سانتیگراد پلیمری گردیدند. نهایتا، توانایی آزاد سازی ۳ پلیمر حاوی دارو در محلول بافر با pH برابر ۱/۳ در دمای ۳۷ درجه سانتیگراد بررسی گردید. طیفهای GPC پلیمرها نشان دادند که پلیره شدن مونومر های حاوی دارو ها انجام گرفته است. نتایج ثابت کردند که این سیستم های پلیمری، توانایی آزاد سازی دارو ها را دارند.

کلمات کلیدی: دارو، مونومر پارا استایرن سولفونیل کلرید، پلیمره شدن، آزاد سازی دارو.

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