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Control drug release delivery of new sulfametazine drug-conjugated poly *p*-styrene sulphonate system

Abbas Amini Manesh[1,*] Ardeshir Khazaei[2,*] and Asieh Asgari[1]

[1]*Department of Chemistry, Payame Noor University,* P.O. Box 19395-4697, *Tehran, I. R. of IRAN*
[2]*Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Iran*

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Abstract

Controlled drug release is one method for Stabilization of the drug concentration and its gradually releasing during the period of cure to make the most desire cure effect with decreasing the drug dose consumption. The application of polymers has been extended in this filed. This study includes the synthesis of p-styrene sulphonyl sulfametazine as monomer from p-styrene sulfonyl chlorid, and then the monomer is polymerized with AIBN (Azobis isobutyro nitrile) by free-radical polymerization mechanism, at the temperature 80 °C. The prepared products were characterized by ^{1}H NMR and IR spectra. Then, the drug release ability of the polymer was test in buffer solution with PH = 1.4 at the temperature of 37°C. The results from the UV absorption of polymer established that, the polymer is able to release drug.

Keywords: controlled drug release, sulfametazine, p-styrene sulphonyl chloride, and polymer.

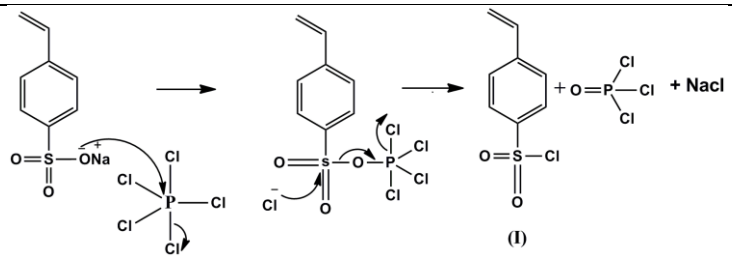
1. Introduction

Drug delivery systems (DDSs) have evoked researchers' interests in the past three decades. The ideal DDSs should be biocompatible and nontoxic, which have high loading capacity, suitable size and sufficient stability to prevent from uptake by reticuloendothelial system and excretion from body. It is also desirable for DDSs to reduce the side effect of drugs on healthy cells and tissues [1].

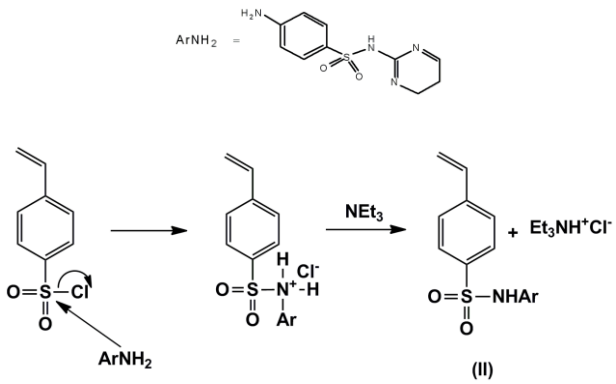
Polymers are increasingly getting important in the field of drug delivery. They can be blended with other low- and high - molecular weight materials, and can be used for any applications. Advances in polymer science have led to the development of several novel drug-delivery systems [2]. The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and the ways in which chemicals or drugs are administered have gained increasing attention in the past two decades. Normally, a chemical is administered in a high dose at a given time only to have to repeat that dose several hours or days later. This is not economical and sometimes results in damaging side effects. As a consequence, increasing attention has been focused on methods of giving drugs continually for prolonged time periods and in a controlled fashion. The primary method of accomplishing this controlled release has been through incorporating the chemicals within polymers. This technology now spans many fields and includes pharmaceutical, food and agricultural applications, pesticides, cosmetics, and household products.

Controlled drug release is, one of the most important methods to increase the therapeutic effects and decrease the side effects of drug. Therefore, it has attracted great interest in recent years and application of polymers has been also extended in this filed [4,5].

Polymers may be used as carriers for pharmaceutical agents [6]. Therefore, the drug is released in certain parts of the body in a required dose and desirable specific rate which itself consists of various techniques [7]. Drug can be released from polymeric carriers by hydrolytic or enzymatic cleavages. The value of the hydrolysis rate constant depends on the strength and chemical nature of the agent- polymer chemical bonds, the polymer structure and the surrounding conditions [8]. Recently, hydrolysis of synthetic macromolecules has been studied [9-11]. In this work, chemically controlled release method has been applied in which the sulfametazine as drug (with -NH_2 active group) linked up to the monomer (p-styrene sulphonyl chloride) by chemical bond and then, the obtained monomer is polymerized by AIBN as an initiator. Finally, hydrolysis reaction was carried out in buffer solution with pH = 1.4 at temperature 37 °C, Scheme 1 and 2. mulsions [3].



Scheme 1. Mechanism of p-styrene sulphonyl chloride synthesis.



Scheme 2: Mechanism of sulfametazine p-styrene sulphonate synthesis.

2. Experimental

2.1. Materials

Sulfametazine (obtained from the Ministry of Health and Medical Education of Iran), 4-vinyl benzene sulphonic acid sodium salt (Fluka AG), tetrahydrofuran (THF), triethylamine (TEA), 2,2-azobis iso butyronitrile (AIBN), chloroform, diethyl ether, magnesium sulfate, potassium chloride, hydrochloric acid, were obtained from Merck.

2.2. Instruments

Infra-red spectra were taken on a PERKIN ELMER spectrophotometer using KBr pellet. 1H NMR spectra were recorded on a JEOL FT-NMR 90 MHz spectrophotometer using DMSO as a solvent. Ultra violet 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. p-Styrene Sulphonyl Chloride Synthesis

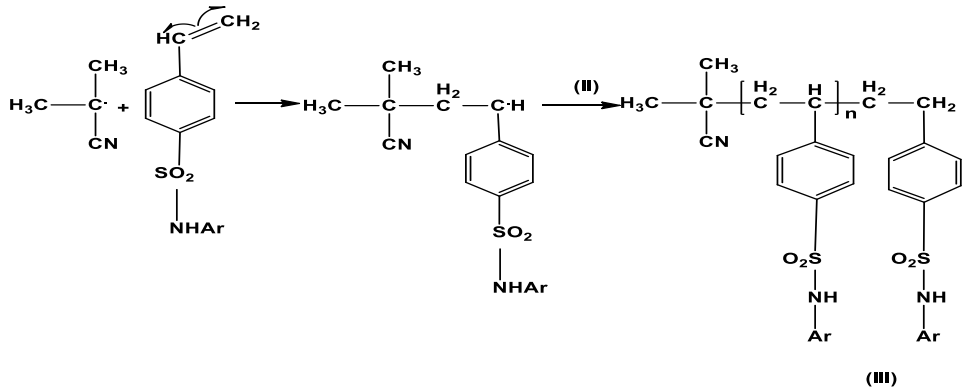
P-Styrene sulphonyl chloride monomer was synthesized by the reaction of 4-vinyl benzenesulfonic acid sodium salt (5 g, 0.024 mol) with PCl_5 (7.5 g, 0.036 mol) in three-necked flask equipped with magnetic stirrer, reflux condenser, and thermometer. The reaction mixture was stirred in ice water bath for 30 minutes 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 a mixyure of 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 CHCl3/water and removing of organic phase, it was dried over anhydrous $MgSO_4$ (Scheme 1).

2.4. Monomer Synthesis

Monomer (II) was synthesized by the reaction of sulfametazine and p-styrene sulphonyl chloride. The mixture of 2.78 g (0.01 mol) of sulfametazine, 10 ml triethylamine and 30 ml of twice distilled THF were poured in a three-necked flask with a reflux condenser, thermometer and a magnetic stirrer. The solution was cooled to 0 °C for 1 h, and then 0.35g (0.01 mol) of prepared p-styrene sulphonyl chloride dissolved in 20 ml of THF was added drop wise. The system was maintained in this condition for 8 h. 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 $MgSO_4$ (Scheme 2). Melting point of the monomer II is 198 °C. The drug-monomer was characterized by the IR and ^{1}H-NMR spectra.

2.5. 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 80-90°C for 15 h. After completion the reaction, solvent was evaporated completely. The polymer was washed with 5% aqueous NaOH and water, then dried with $MgSO_4$ (scheme 3). The melting point of the polymer is 255 °C. The IR and ^{1}H NMR spectra confirmed that the polymer was synthesized (III).

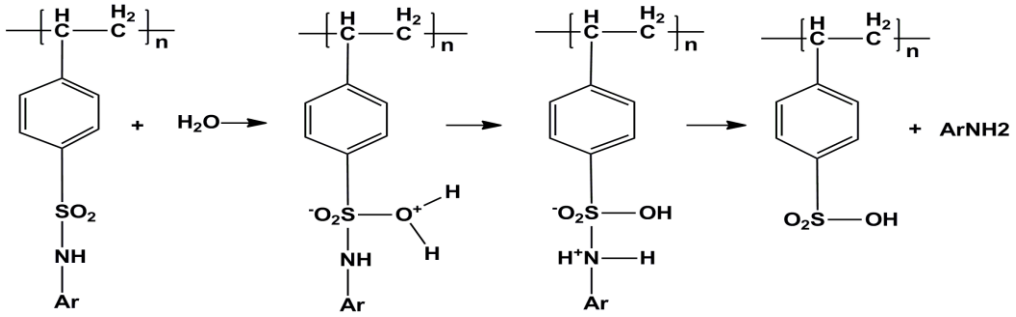


Scheme 3: Mechanism of poly (sulfametazine p-styrene sulphonate) synthesis.

3. Drug release study

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 6 test tubes and then 25 ml of buffer solution with pH = 1.4 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 table 1, the test tubes were withdrawn from the water bath and 2 ml of 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 (figures 1 and 2).

Absorbance of sulfametazine was measured at λ_{max} = 240 nm. The results of the UV spectra of the hydrolyzed polymer are depicted in figure 3.



Scheme 4. Mechanism of polymer-sulfametazine hydrolysis in buffer solution.

Table 1. Hydrolysis result at 37 °C

Sample	Concentration(ppm)	Absorption	Time(hr)
1	0	0	0
2	43.71	0.332	20
3	94.10	0.715	24
4	146.61	1.114	48
5	160.81	1.222	72
6	170.28	1.294	85
7	197.57	1.471	118

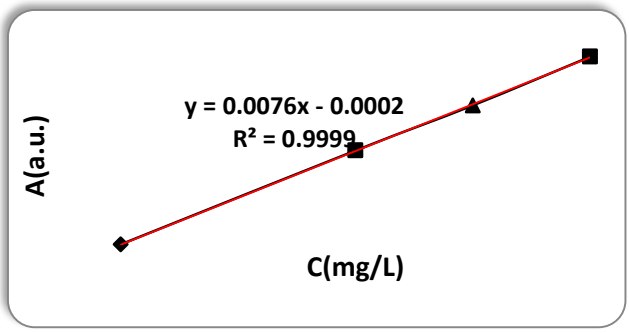


Figure 1. Standard curve of sulfametazine.

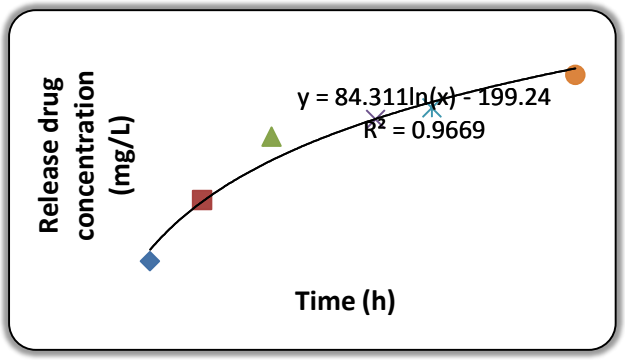


Figure 2: Hydrolysis profile of polymer-sulfametazine at 37 °C.

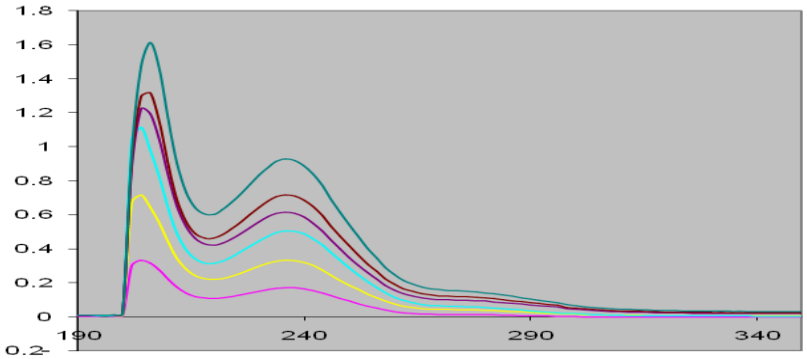


Figure 3: UV spectra of obtained samples after hydrolysis at 37 °C.

4. Results and discussion

The IR and ^{1}H NMR spectra of monomer are as following: IR (KBr): 3445 cm^{-1} (N-H), 2939 cm^{-1} and 2977 cm^{-1}(aromatic C-H) , 1632 cm^{-1} (C=N), 1338 cm^{-1} (asymmetric SO_2), and 1169 cm^{-1} (symmetric SO_2). ^{1}H NMR (90 MHz, DMSO): δ = 8.43-7.01 ppm (m, 10H, aromatic hydrogen, and CH_2=CH-Ph); δ =5.93- 5.33 ppm (m, 1H, CH=N); δ = 3.99-1.17 ppm (m, 5H, CH=Ph and CH_2-CH_2).

The IR and ^{1}H NMR spectra of polymer are as following: IR (KBr): 3324 cm.$_1$(N-H), 2940 cm^{-1} (aromatic C-H), 1345 cm^{-1} (asymmetric SO_2), 1164 cm-1 (symmetric SO_2). ^{1}H NMR (90 MHz, DMSO): δ = 8.06-6.43 ppm (b., aromatic C-H, CH=N); δ =3.41 ppm (b., CH_2-CH_2); δ = 1.02 ppm (b., CH_2-CH-Ph).

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 [12]. 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 average molecular weight of polymer containing sulfametazine was determined by GPC and found to be 239103.

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. Scheme 4 indicates the mechanism of hydrolysis of S-N bond of synthesized polymer in buffer media. The synthesized compound can be used as controlled drug delivery systems for medicinal applications.

5. Conclusion

In this system the functional group of the drug, is covalently attached to the backbone of polymer. The Monomer (II) was synthesized by the reaction of p-styrene sulphonyl chloride and sulfametazine, and the polymer containing drug (III) was produced from polymerization of this monomer by AIBN.

The molecular weight of obtained polymer was 239103. Drug release tests in buffer solution at temperature 37 °C showed that the polymer is able to release drug. So the synthesized compound can be used as controlled drug delivery system for medicinal applications.

6. Acknowledgement

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