Variables affecting sulfasalazine - ion exchange resin complexation

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Abstract:

The aim of this work is studying the effect of different variables on the loading of sulfasalazine on DEAE sephadex A 25 ion exchange resin as a carrier for systemic action. Different drug: resin complexes (resinate) of different ratios (2:1, 1:1, 1:2, 1:4, 1:6) were prepared, dionized distilled water used to prepare sulfasalazine solution, and their entrapment efficiency was estimated through changing variable conditions including temperature of stirring, stirring time, stirring speed, pH. The best complex was formed using 1:6 drug: resin ratio prepared at 50 ºC, stirring speed 400 rpm for 120 minutes in deionized water (pH 7). The prepared complex gave 77.8% drug release within 15 minute and continued up to 97.613% within 75 minute upon exchanging the drug with ions of similar charge in the dissolution medium (phosphate buffer pH 7.4).

Key words: DEAE sephadex A 25 ion exchange resin, sulfasalazine.

المتغيرات التي تؤثر على ترابط السلفاسالازين و راتنج التبادل الأيوني

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الخلاصة:

الهدف من هذا العمل هو دراسة تأثير المتغيرات المختلفة على تحميل مادة السلفاسالازين على راتنج التبادل الأيوني (DEAE sephadex A 25) باعتبارها حامل للدواء للعمل داخل الجسم. تم تحضير مركبات راتنج دوائي (راتنجيات) مختلفة بنسب مختلفة من الدواء: الراتنج (٢: ١ ، ١: ١ ، ١: ٢ ، ١: ٤ ، ١: ٦), باستخدام الماء المقطر منزوع الايونات لتحضير محلول السلفاسالازين, وتم تقدير كفاءة تحميل الدواء من خلال تغيير الظروف بما في ذلك درجة حرارة التحريك ، وقت التحريك ، سرعة التحريك ، درجة الحامضية أفضل مركب تكون باستخدام نسبة دواء: راتنج ١: ٦, والتي حضرت عند ٥٠ درجة مئوية ، مع سرعة تحريك بلغت ٤٠٠ دورة في الدقيقة لمدة ١٢٠دقيقة في ماء منزوع الأيونات. ولقد حرر هذا المركب المحضر ٧٧,٨ % من الدواء في غضون ١٥ دقيقة واستمر حتى حرر ٩٧,٦١٣٪ من الدواء في غضون ٧٥ دقيقة وذلك عند تبادل الدواء مع الايونات ذات الشحنة المماثله له في وسط الذوبان (محلول بفر الفوسفات بدرجة حموضة ٧,٤).

الكلمات المفتاحية: راتنج التبادل الايوني السيفادكس, السلفاسالازين

Introduction

The manufacturing of drug dosage form today is focused on developing an optimized products with maximum therapeutic effectiveness with minimum side effects [1] . By using suitable ion exchange resin the eluting of active agents may still constant over a long period, so it may trigger by environment or other external events to achieve highest effective therapies while decreasing the potential of under and overdosing[2]. The drug-resin complex was formed when drug solution has been kept in contact with ionic resin. The drug releases from the complex by exchanging with ions present in

gastrointestinal tract (Na^+ and Cl^- ions) when is taken orally. These systems generally utilizing resin compounds which is water insoluble cross linked polymer that contain salt forming functional group in specific positions located on the polymer chain[3] . The diffusion rate of drug out of the resin complex is sustained by the area of diffusional path length and types of resin which depend on the degree of cross-linking agent used to prepare resins also [4]. Selecting the resin for a specific application requires consideration of number of factors mainly the charge type (cation or anion exchanger). If a rapid dissolution is desired, weak cation or anion exchangers with small particle size and low degree of cross-linkage, should be considered, while slow or gradual release or maximum taste protection/masking can be obtained by using strong cation or anion resins with large particle size and high degree of cross-linkage. If maximum potency is a priority with a low molecular weight drug, a resin with a high exchange capacity may be chosen. the resin with high molecular weight have a limited ability to sorb the drug so it should be with very low degree of cross-linkage to achieve a meaningful drug loading[5].

Sulfasalazine is tasteless, odorless, brownish-yellow powder and practically insoluble in water and very slightly soluble in ethanol(6). It was used in the treatment of inflammatory disease and has antitumor effect due to inhibition of uptake of extracellular cystine (or the reduced form cysteine) by cancer cells. Cysteine is essential for maintaining the glutathione (GSH) level which has a regulatory role in cell replication, therefore lead to subsequent growth arrest [7, 8].

Sephadex ion exchange resin (DEAE Sephadex A-25 a weakly basic anion exchanger) is white spherical particles with particle size 40-120µ. Sephadex ion exchangers are insoluble in all solvents. They are stable in water, organic solvents, alkaline and weakly acidic solutions (9). It is suitable to use as drug carrier to induce emboli in the targeted artier (10).

The aim of this work is to study the loading of sulfasalazine on the sephadex ion exchange resin and optimize the complex formation to be used as a carrier that can exchange the drug with ions of similar charges available in the systemic circulation [11], which give the systemic therapeutic action of the drug.

Materials and Methods

Materials

Sulfasalazine purchased Hyperchem, China. Poly vinyl alcohol from Central Drug House, new delhi, India. DEAE-sephadex A25 from Pharmacia Pharmaceutical company, Sweden. Potassium dihydrogen orthophosp and sodium hydroxide from Sd fine-Chem limited, Mumbai, India.

Methods

Preparation of Drug-Resin Complex

The drug-resin complex has been prepared by adding the resin to the sulfasalazine aqueous solution (300 ml) with continuous stirring using magnetic stirrer. Different amount of resin was used to prepare different drug: resin ratios 2:1, 1:1, 1:2, 1:4, and 1:6, different mixing time, stirring speed, processing temperature have been study for each ratio. Then each mixture had been filtered and allowed to dry in a hot air oven at 40 ºC overnight [12]. The drug entrapment efficiency for each ratio had been determined by analyzing the filtrate for the free drug at 359 nm UV absorbance, and the amount of sulfasalazine entrapped was determined by indirect method according to the following equation [13].

Entrapment efficiency (EE) = entrapped drug content (initial amount of drug- free amount of drug) / initial drug content

Effect of mixing time on the entrapment efficiency of drug

The drug: resin complexation in deionized water in all ratios was carried out by

stirring the mixture for 30, 60 and 120 minutes using magnetic stirrer at room temperature and 200rpm stirring speed [14].

Effect of stirring speed

Different stirring speed 200, 300, and 400 rpm applied for all the prepared drug: resin mixture in deionized water in all ratios for 120 minute at room temperature (25 ºC) [15].

Effect of temperature

The prepared drug: resin mixture in deionized water in all ratios had been stirred at three different stirring temperatures (25, 40 and 50 ºC) at 400 rpm stirring speed for 120 minute using hot plat magnetic stirrer [16].

Effect of pH on the entrapment efficiency of drug

Drug: resine mixture in all ratios was prepared in phosphate buffer solutions of different pH values (6, 7.4 and 8) instead of deionized water at 400 rpm stirring speed and 50 ºC for 120 minutes[17].

In-vitro dissolution study for the selected drug: resin complex

The release of the drug from selected drug: resin complex (resinate; 1:6) was studied using dissolution apparatus II and 900 ml phosphate buffer at pH 7.4 (physiological pH of blood) fixed at 50 rpm stirring speed and 37 ºC (). Samples (5ml) were withdrawn at predetermined time, filtered and analyzed using UV spectrophotometer at 359 nm [18], the withdrawn samples were replaced by the same volume of fresh phosphate buffer [19].

Fourier transform infrared (FTIR)

Samples of drug (sulfasalazine), DEAE sephadex A25 and selected drug-resin complex (resinate) each one separately were mixed with sufficient quantity of KBr and compressed into a disk then analyzed using a FTIR spectrometer. Scanning range was 4000-400 cm^{-1} [20], to determine the interaction between drug and polymer system if present.

Statistical analyses

Statistical analysis was done by using one-way analysis of variance (ANOVA) and independent sample t-test. The differences were considered statistically significant when ($P < 0.05$). All data analysis was performed using spss 16 software.

Result and discussion

Preparation of Drug-Resin Complex (resinate)

DEAE sephadex A 25 is one type of the anion exchange resins, which is a weak base in nature and suitable for formation of complex with sulfasalazine since it is a weak acid drug [9]. Sulfasalazine- DEAE sephadex A 25 complex was prepared in different ratios to choose the optimum drug: resin ratio based on entrapment efficiency. Figure (1) shows entrapment efficiency for the drug in each drug resin complex ratio. The results showed that as the amount of resin increased the entrapment efficiency was increased and the optimum ratio was 1:6 where the entrapment efficiency was 43.04 % (stirring for 120 minutes, 300 rpm stirring speed at 50 ºC), this may be due to increase in the total number of chemical equivalent($NH^{+}(CH_2CH_3)_2$) that available for ionic exchange (cl^{-} exchange with the sulfasalazine union in complexation process and verse versa inside human body) per unit weight or volume of resin[21].

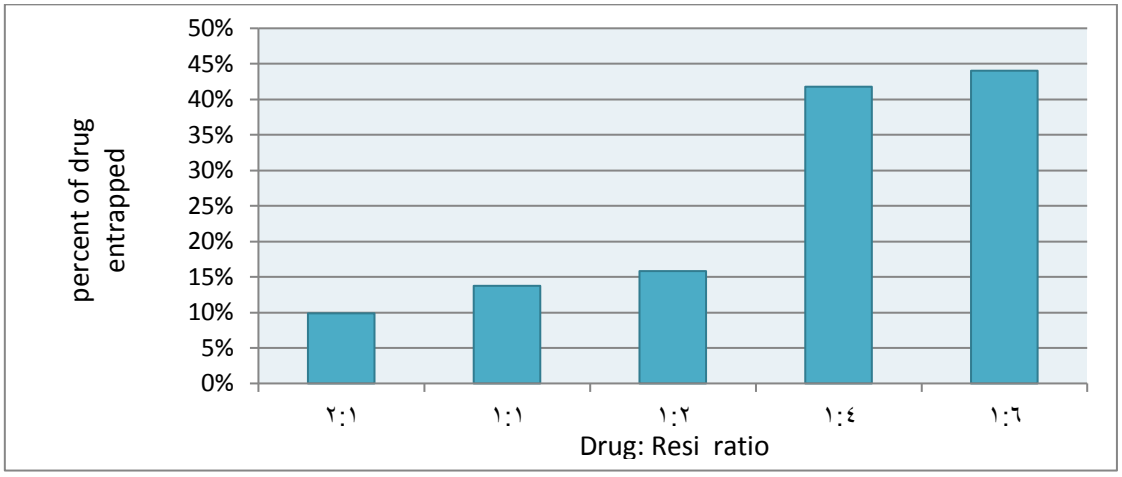
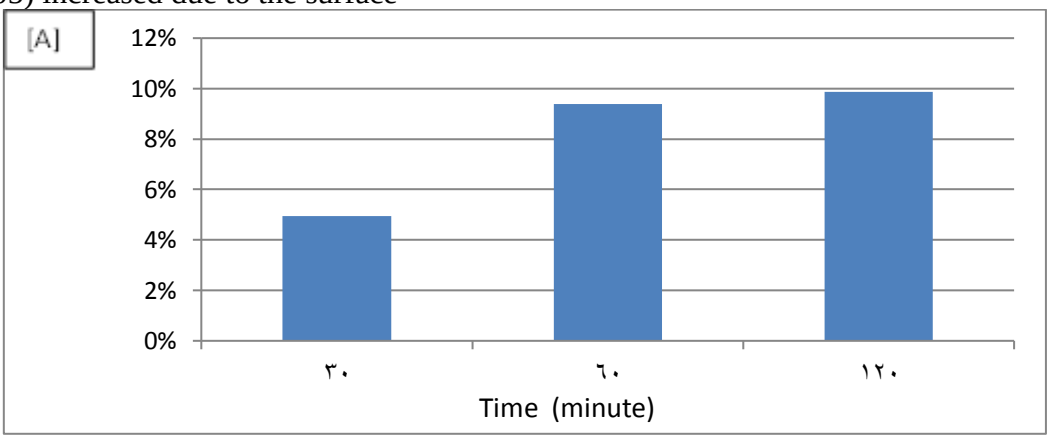
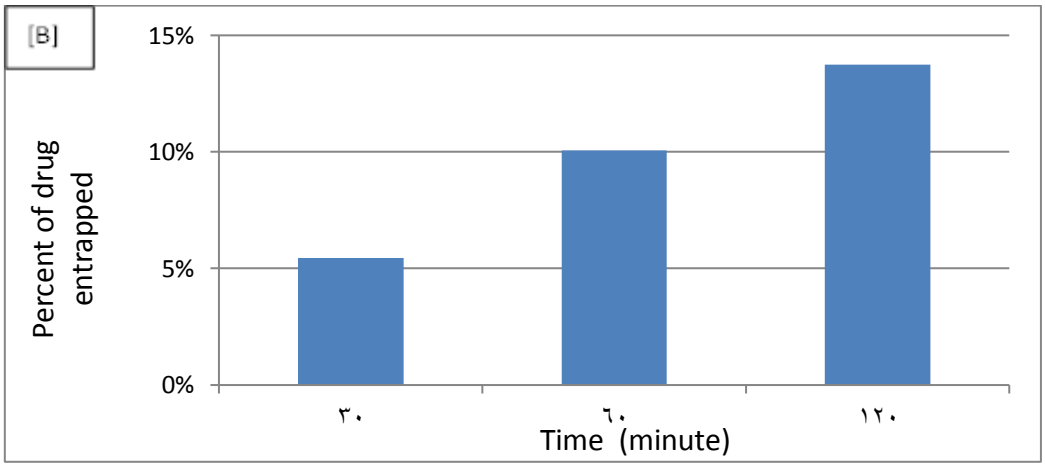


Figure (1): Entrapment efficiency for different drug: resin ratio variables effecting entrapment efficiency of the drug on DEAE sephadex A2

Effect of mixing time

Using different mixing time on entrapment efficiency for drug: resin mixture in all ratios (2:1, 1:1, 1:2, 1:4, 1:6) showed that upon increasing the stirring time the entrapment efficiency was significantly ($P<0.05$) increased due to the surface absorptive phenomenon" the adhesion of atoms, ions or molecules from a gas, liquid or dissolved solid to a surface which creates a film of the adsorbate on the surface of the adsorbent" [22]. As shown in Figure (2 A, B, C, D and E).





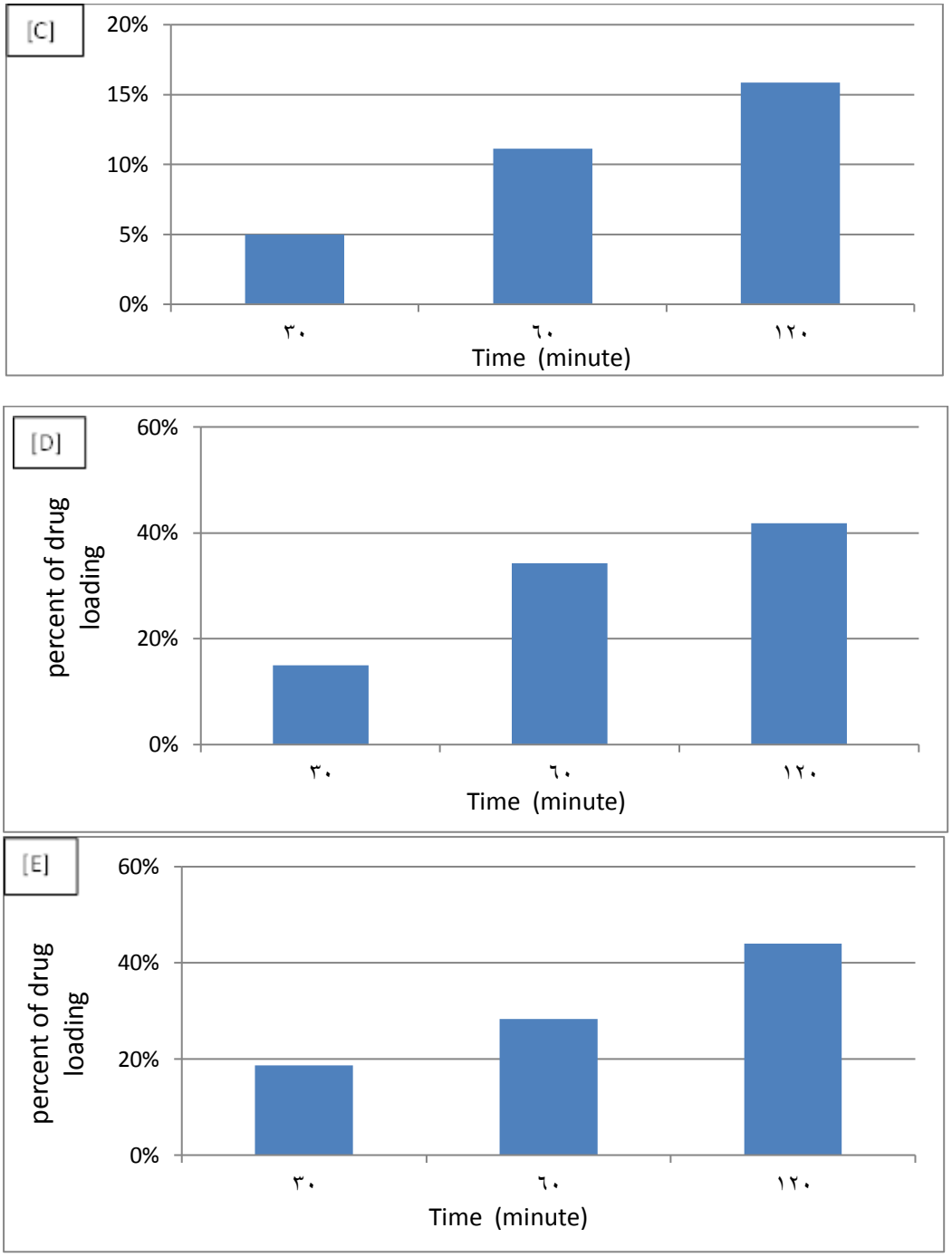


Figure (2) Effect of mixing time on entrapment efficiency of sulfasalazine in different drug: resin ratios (A) ratio2:1, (B) ratio1:1, (C) ratio1:2, (D) ratio1:4, (E) ratio1:6.

Effect of stirring speed

At drug: resin ratio 1:1, 1:2, it was found that as the stirring speed increased from 200 to 300 rpm, the entrapment efficiency was significantly ($P< 0.05$) increased in comparison to ratio 2:1 because the amount of resin was increased and so need high stirring speed to maintain the dispersed phase and prevent the sedimentation of resin[23]. While upon further increase in stirring speed from 300 to 400 rpm, the entrapment efficiency was decreased since the excessive stirring speed may lead to sticking of resin to wall of the container [24]. For higher drug: resin ratios 1:4,1:6, it was found that as a stirring

speed increase the entrapment efficiency significantly (P< 0.05) increase because the agitation speed ensured better interactions between the resin and drug , especially when the amount of resin is high as explained previously [25], The same results was observed with removal of toxic metal ions using chemically modified guar gum sulphonic acid [26]. as shown in Table (1)

Table (1): Effect of stirring speed on entrapment efficiency of sulfasalazine in different drug: resin ratios

Drug: resin ratio	Entrapment efficiency of drug at different stirring speed		
	200 rpm	300 rpm	400 rpm
2:1	10%	8%	7%
1:1	10%	16%	14%
1:2	17%	20%	18%
1:4	28%	39%	41%
1:6	38%	43%	46%

Effect of temperature

It was found that upon increasing the processing temperature the entrapment efficiency was significantly (P< 0.05) increased due to increase in the solubility of the drug, the higher temperature tends to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone, as well as increased temperature during complexation increases ionization of drug and resin. [27], as shown in Table (2)

Table (2): Effect of temperature on entrapment efficiency of sulfasalazine in different drug: resin ratios

Drug: resin ratio	Entrapment efficiency of drug at different temperature		
	25 °C	40 °C	50 °C
2:1	**6%**	**8%**	**10%**
1:1	**11%**	**16%**	**19%**
1:2	**16%**	**17%**	**21%**
1:4	**29%**	**35%**	**39%**
1:6	**32%**	**43%**	**55%**

Effect of pH

Using buffer solutions of different pH (6, 7.4, 8) instead of deionized distilled water (as a dispersed media) showed a significant (P< 0.05) decrease in entrapment efficiency that may be due to the presence of ionic fractions for phosphate buffer solution which can compete with the drug ions on resin functional group. The results also showed an increased entrapment efficiency at (pH 6) in comparison to pH 7.4 and pH 8 because at higher pH the drug adsorption decreased since more ($H_2PO_4^-$) was available in the environment that competitively decreasing the drug ions binding [25].as shown in table (3)

Table (3): Effect of pH on entrapment efficiency of sulfasalazine in different drug: resin ratios in comparison to deionized water

Drug: resin ratio	Entrapment efficiency of drug at different pH and deionized water			
	pH 6	pH 7.4	pH 8	Deionized water
2:1	11%	5%	5%	10%
1:1	14%	6%	8%	19%
1:2	14%	8%	11%	21%
1:4	14%	9%	11%	39%
1:6	17%	2%	12%	43%

In-vitro dissolution study for the selected drug: resin complex

According to the results concerning entrapment efficiency, the best drug: resin complex ratio 1:6 was selected and prepared with optimum conditions (120-minute mixing time, 400 rpm stirring speed at 50 ºC in deionized distilled water). Figure (3) shows the cumulative percent of drug release for the selected drug: resin ratio 1:6. The results showed that the percentage of sulfasalazine released within 15 minutes at phosphate buffer (pH 7.4) was 77.8 %, and the release continued up to 97.613% within 75 minutes, this may be due to the fact that the complex will release the drug only when it is replaced by the ions which have the same charge ($H_2PO_4^-$) after hydration of drug: resin complex by the medium. The ionic exchange may reach equilibrium, and this depend on the ionic constitution and the fluid volume, also the drug must diffuse from the resin through the internal exchange sites and it mainly depends on the efficient complex formed between the drug and the resin[28].

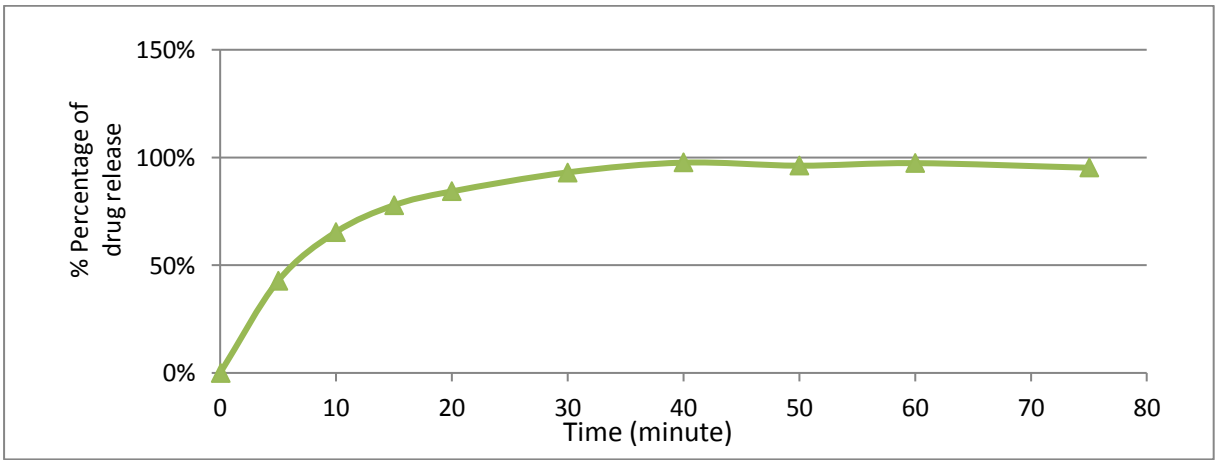


Figure (3): Percentage of drug release of selected drug: resin ratio (1:6) with best entrapment efficiency

Fourier transform infrared (FTIR)

Figure (4) shows the FTIR spectrum of the pure sulfasalazine, the spectra displayed broad peaks between 2500 cm^{-1} to 3100 cm^{-1} which are related to stretching vibration of (O-H) carboxyl group and (N-H) bond and at 1700 cm^{-1} which are related to stretching vibration of (C=O)carboxylic acid group, whereas the sharp peak at 1645 cm^{-1} resulted from bending vibration of N=N bond, and intense two peaks at 1200 cm^{-1} and 1400 cm^{-1} which are related to stretching vibration of two (S=O) of sulfonic group. The spectrum was identical with reported spectrum for the drug [29].

The FTIR spectrum of the DEAE sephadex A25 is shown in figure (5), the peak at 2930 cm^{-1} is related to aromatic C-H stretching vibration and broad peak from 3200 cm^{-1} to 3600 cm^{-1} as a result of stretching vibration of alcohol O-H bond and N-H bond, while the broad peak at 1637 cm^{-1} representing the aromatic C=C stretching, whereas the peak at 1367 cm-1 is related to stretching vibration of C-N bond, and the peaks at 1020 cm^{-1} and 1120 cm^{-1} representing the C-O bond stretching. The spectrum was identical with that reported for the resin [30].

Figure (6) showed the FTIR spectrum of the selected sulfasalazine-DEAE sephadex A25 complex (resinate). The intense broad peak at 3200 cm^{-1} to 3600 cm^{-1} related to stretching vibration of N-H bond and the peak at 1700 cm^{-1} related to carboxylic C=O stretching of the sulfasalazine was disappeared indicating the formation of drug- resin complex by the ionic bond formation between the carboxylic group of sulfasalazine and amide group of DEAE sephadex A 25 [31].

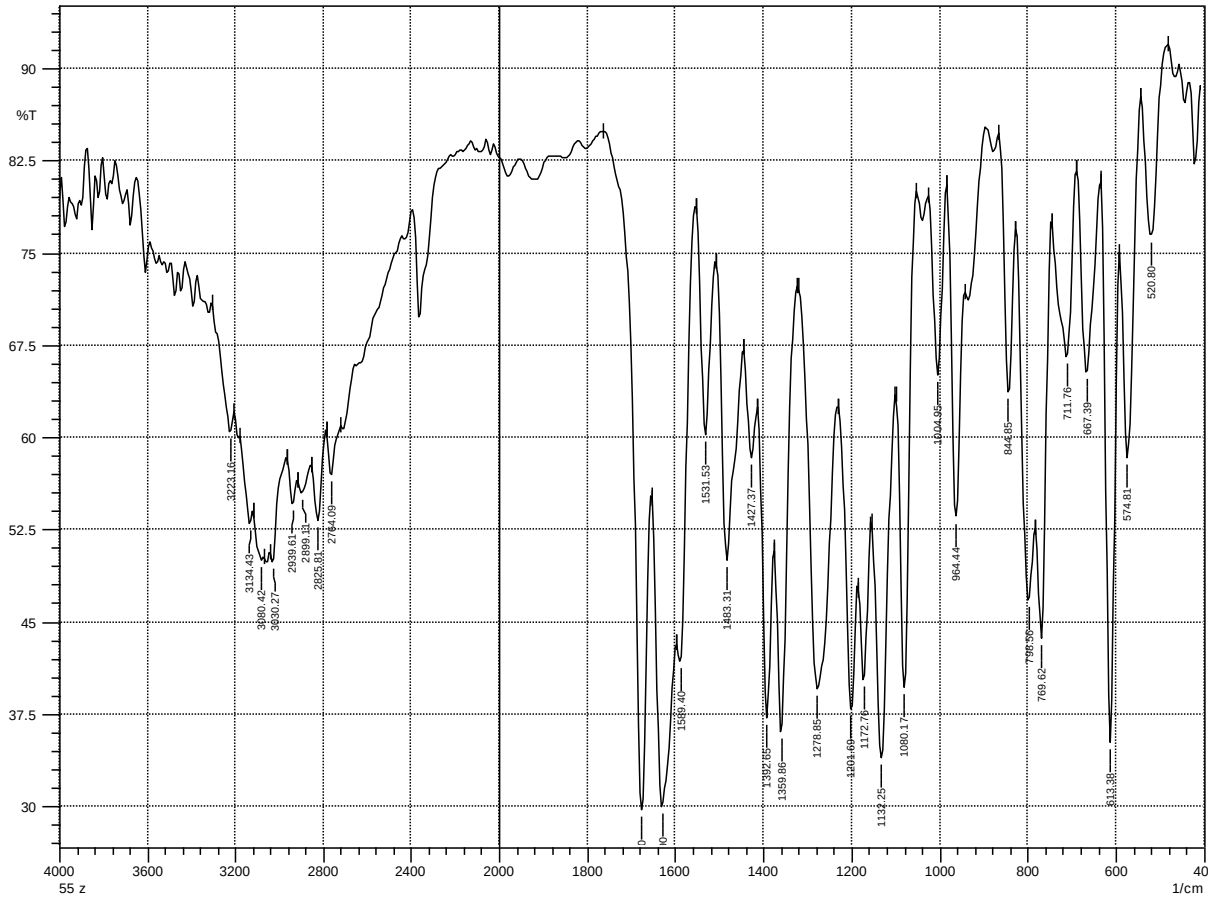


Figure (4): FTIR spectrum of sulfasalazine

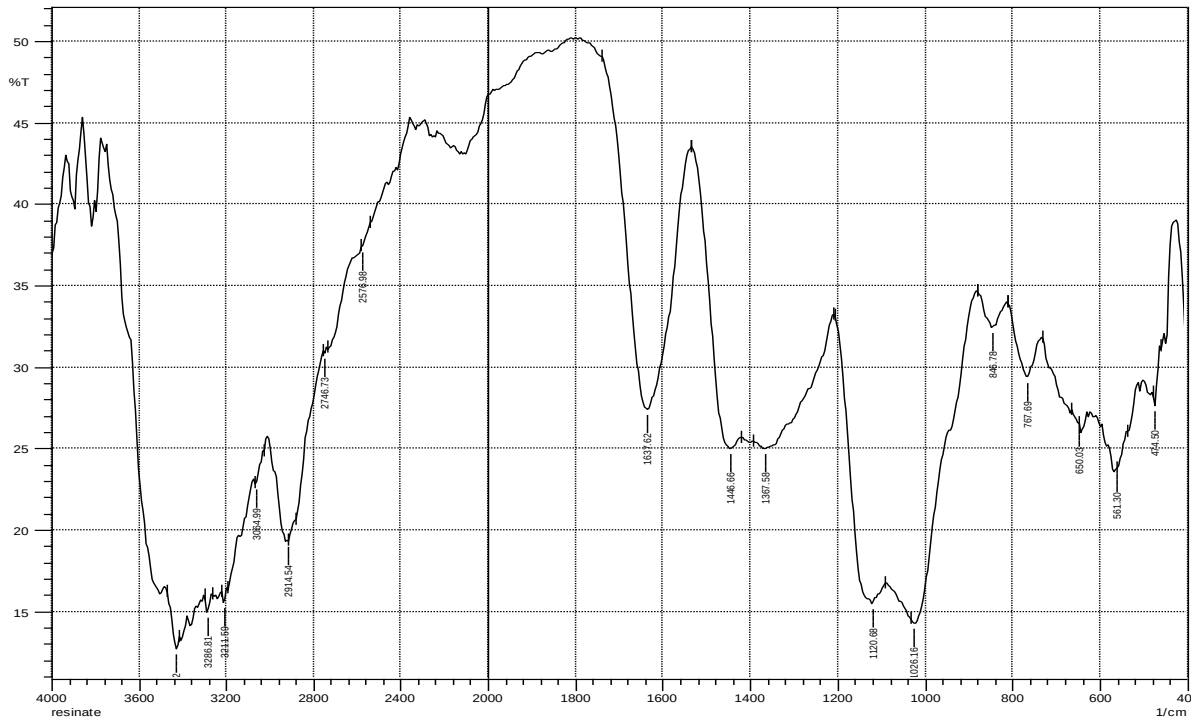


Figure (5): FTIR spectrum of DEAE sephadex A25 resin

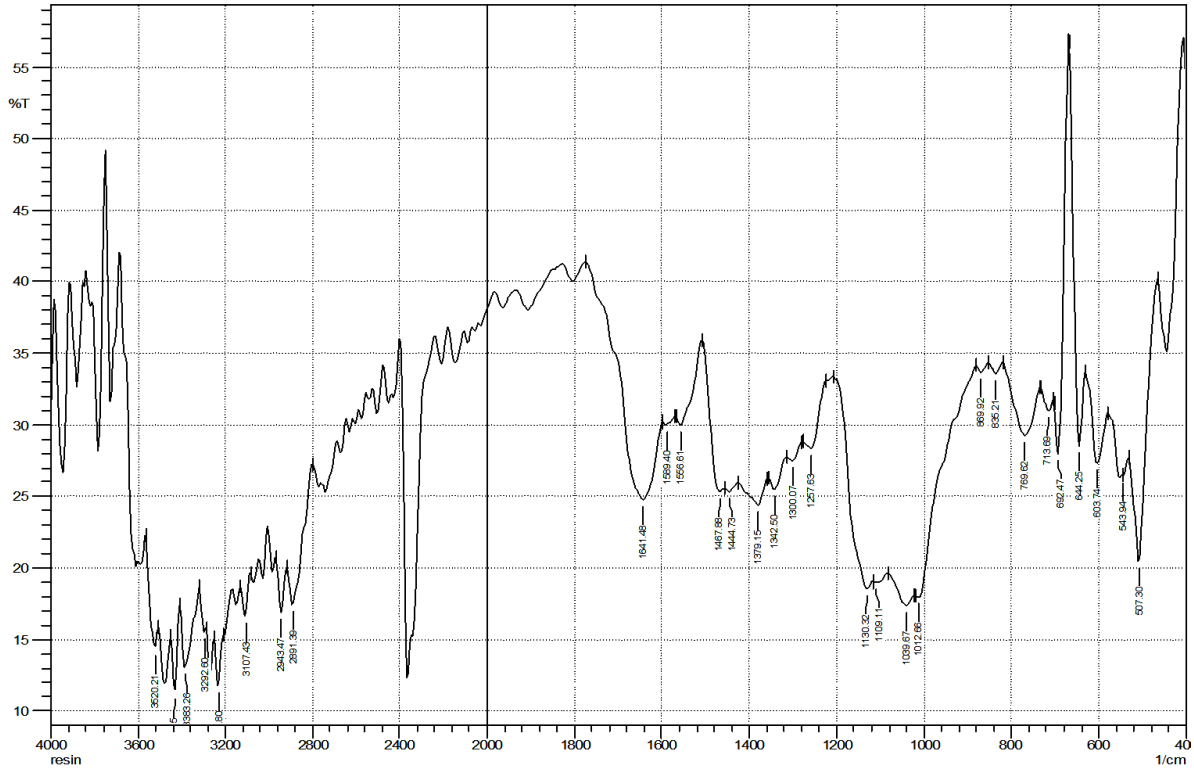


Figure (6): FTIR spectrum of selected resinate (drug: resin ratio 1:6)

Conclusion

Ion- exchange resin DEAE sephadex A 25 can be used effectively as a carrier for sulfasalazine to be used for injectable therapeutic purposes though drug- resin complex between the carboxylic group of the drug and the amide group of the resin.

The entrapment efficiency of drug in resin was highly affected by drug: resin ratio, stirring time, temperature using deionized water as a dispersion medium. The drug was released in vitro from the complex by replacing with ions having the same charge (Cl-, OH-) in the dissolution medium so the drug can give its therapeutic action.

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