

Chlorosulfonation of Acetanilide to Obtain an Intermediate for the Preparation of a Sulfa Drug

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Abstract

Aim: The major scope of the work is to find best suitable conditions and process for the preparation of sulfa drug where the yield can be maximum with reduced periods. **Materials and Methods:** Sulfathiazole is prepared by chlorosulfonation of acetanilide (at 114°C) to obtain an intermediate which is reacted with 2-aminothiazole. The samples of intermediate and 2-aminothiazole with ratios (3:1, 1:1, and 1:3) and with different acid acceptors named pyridine, sodium bicarbonate, dimethylaniline, and ammonium hydroxide are studied. **Results and Discussion:** Chlorosulfonation at 114°C yielded good which further gave good results (91% yield) with 3:1 intermediate and 2-aminothiazole concentration and pyridine as an acid acceptor. The analysis was performed using infrared (IR) spectroscopy in Fourier transform IR spectroscopy which is found to be the best method for identification of samples. **Conclusions:** Among the reaction ratios studied for sulfathiazole, sample with 3:1 ratio of p-acetamidobenzenesulfonyl chloride to 2-aminothiazole with pyridine as an acid acceptor is proved to be the best reactant ratio with yield 91.34%. The process employed for experimentation proved to be an efficient and time-saving process.

Key words: Acetanilide, chlorosulfonation, fourier transform infrared spectroscopy, p-acetamidobenzenesulfonyl chloride, pyridine, sulfathiazole

INTRODUCTION

Sulfonamides were the first effective chemotherapeutic agents employed systematically for the prevention and cure of bacterial infections in humans. They were classified as the first real “wonder” drug developed.^[1] After the introduction of penicillin and other antibiotics, the popularity of sulfonamides decreased. However, they are still considered useful in certain therapeutic fields, especially in the case of ophthalmic infections as well as infections in the urinary and gastrointestinal tract. Sulfathiazole (4-amino-N-2-thiazolylbenzenesulfonamide) is clinically one of the most used. Sulfonamide is the basis of several groups of drugs. They are bacteriostatic antibiotics that competitively inhibit the conversion of p-aminobenzoic acid to dihydropteroate, which bacteria need for folate synthesis and ultimately purine and DNA synthesis. For preparation of sulfathiazole,^[2,3] many methods are available in the present day trend but many of the processes do not offer

maximum efficiency. The main aim of the work is to develop a method which gives maximum yields with reduced time and cost efficient when compared to literature. These processes were divided into three steps for proper understanding where the first step is chlorosulfonation^[4] of acetanilide which results in an intermediate p-acetamidobenzenesulfonyl chloride. In the present investigation, it was found that proper mixture of acetanilide and chlorosulfonic acid is required for a good quality of intermediate. Hence, a trial run was made at different temperatures up to 114°C till the best sample is obtained. Then, the second step was the preparation of sulfathiazole [Figure 1] from the obtained intermediate by

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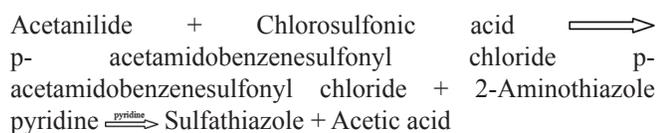
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varying the quantities of intermediate and amine and varying different acid acceptors such as pyridine. The third step was recrystallization of sulfathiazole to obtain purer product. All the identifications of samples were performed using infrared (IR) spectroscopy with Fourier transform IR (FT-IR).^[5]

Process reaction [Figure 2]



MATERIALS AND METHODS

Materials and equipment

Acetanilide (Hychem Labs.), chlorosulfonic acid (Uv scientifics), p-acetamidobenzenesulfonyl chloride (Virchow Laboratories, Hyderabad), 2-aminothiazole (Hychem Labs.), pyridine (Hychem Labs), sodium bicarbonate, Acid Acceptors: Pyridine (Hychem Labs), Sodium bicarbonate, Ammonium Hydroxide, Di-methylaniline, Sodium Hydroxide, Hydrochloric acid, and Sulfathiazole (Hychem Labs.).

FT-IR spectrophotometer (Shimadzu-1800), melting point apparatus (Griffin), complete glass reflux apparatus, heated

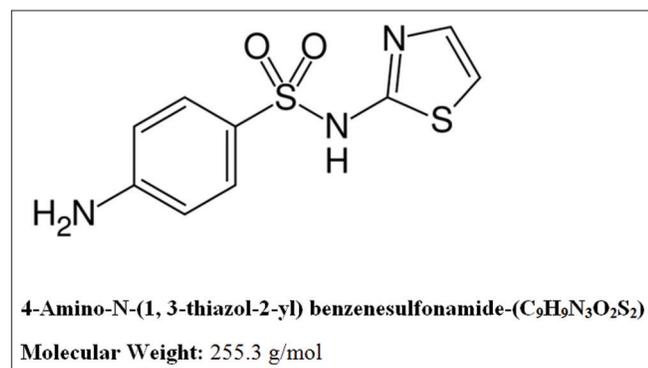


Figure 1: Structure of sulfathiazole

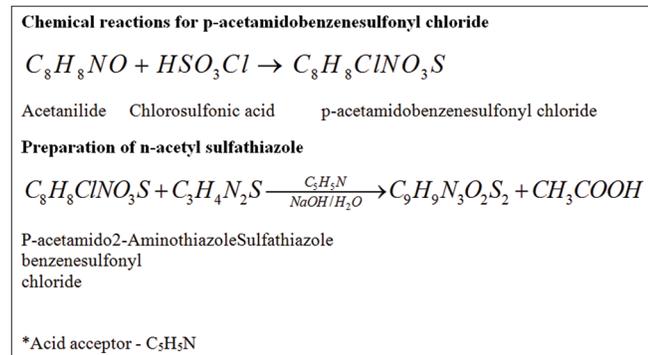


Figure 2: Complete reaction of sulfathiazole

magnetic stirrer with contact thermometer (Remmi), and oil bath with magnetic fish (Corning pc-351).

Synthesis

Chlorosulfonation of acetanilide (preparation of p-acetamidobenzenesulfonyl chloride)^[6]

This is the first step of the processes where required amount of acetanilide is reacted with chlorosulfonic acid to obtain an intermediate called p-acetamidobenzenesulfonyl chloride. This mixture is made to react in a reflux condenser for about 15-20 min where a semisolid paste is obtained which is brown. This step was conducted at different temperatures from 98°C to 114°C because proper melting of acetanilide gave an outstanding output.

Preparation of {4-amino-N-(1,3-thiazol-2-yl) benzenesulfonamide}^[7,8]

This is the second step of the process. 4-aminothiazole reacts with p-acetamidobenzenesulfonyl chloride with different compositions, and different acid acceptors (pyridine, sodium bicarbonate, ammonium hydroxide, and dimethylaniline) were considered and refluxed for about 45 min at 95°C.

Acid acceptors: Acid acceptance has long been a primary function for vapor degreasing solvent stabilizer systems. Acid acceptance provides for the neutralization and removal of hydrochloric acid (HCL) from the degreasing operation. HCL is formed if the solvent breaks down. The acid acceptor reacts with the HCL and removes it by forming insoluble compounds. The insoluble compounds are typically removed with the contaminated solvent.

Recrystallization of obtained sulfa drug (sulfathiazole)^[9]

To crude sulfathiazole, ethyl alcohol is added and boiled below 78°C and cooled. The obtained recrystallized product is primarily investigated using melting point apparatus and was observed that the product obtained has melted at 201-202°C. Hence, it was confirmed that the obtained product was sulfathiazole which is compared to pure sulfathiazole (IP grade).^[10] This same process was applied for different compositions of 2-aminothiazole and p-acetamidobenzenesulfonyl chloride for different acid acceptors (3:1, 1:1, and 1:3).^[11] The obtained 12 samples were investigated using melting point apparatus, and three best samples (one from each composition) were chosen and were further investigated using FT-IR spectrophotometer for which results were reported.

Analysis of the samples

FT-IR spectrophotometer^[12,13]

Standard and sample preparation: Sample/KBr ratio: Thin

pellets were prepared with known amount of sample and KBr. A pellet is much thicker than a liquid film, hence a low concentration of the sample is used, and too high concentration usually causes difficulties obtaining clear pellets. The sample is then inserted on the thin glass film which is homogeneous and transparent. The sample is inserted into the IR holder and the spectrum is made to run. The pure intermediate and sulfathiazole pellets were prepared at different concentrations 10, 20, 30, and 40 μg and also the samples were prepared in the same procedure.

RESULTS AND DISCUSSION

The following melting point tests were carried out for each single sample obtained.

Melting point test for p-acetamidobenzenesulfonyl chloride

Five different samples operated at different temperatures ranging from 98 to 114°C were synthesized, and melting point test is performed for all the samples. Out of all the samples, the one which is reacted at 114°C is melted completely at 144°C during the test which is same as standard melting point temperature of p-acetamidobenzenesulfonyl chloride. Hence, it is found that reaction between acetanilide and chlorosulfonic acid is complete at 114°C and also at this sample gave maximum yield when compared to those at low temperatures. Thus, the intermediate obtained from this sample is of good quality. Percent yield obtained for this particular sample of p-acetamidobenzenesulfonyl chloride is 90.05% [Figure 3]. Further, this sample is selected for FT-IR identification [Table 1].

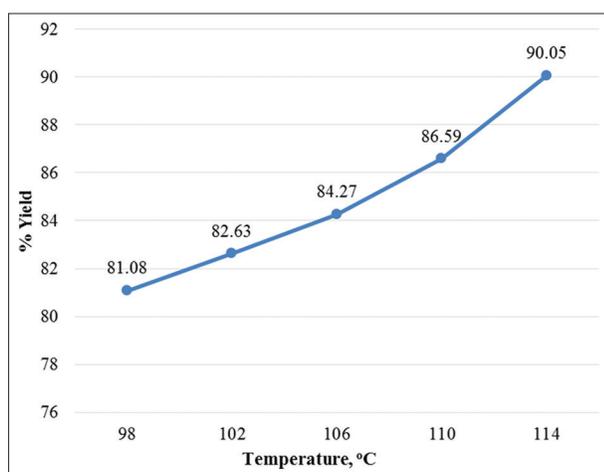


Figure 3: Yields of intermediate observed at varied temperatures. Acetanilide and chlorosulfonic acid are made to react with each other at different temperatures; yields are plotted for the corresponding temperature

Melting point test of sulfathiazole (with 3:1, 1:1, and 1:3 ratios of p-acetamidobenzenesulfonyl chloride to 2-aminothiazole)

All the 12 samples were synthesized with different compositions of intermediate and 2-aminothiazole with different acid acceptors. Melting point test was performed for all the samples, and the melting temperatures were noted and tabulated [Table 2]. Standard sulfathiazole melts at 202°C. Based on the theoretical yield, the weight of crude sulfathiazole is calculated and then the product is

Table 1: Yields of intermediate observed at varied temperatures of acetanilide

Varied temperatures for acetanilide temperature at (°C)	% yields obtained for intermediate (recrystallized)
98	81.08
102	82.63
106	84.27
110	86.59
114	90.05

p-acetamidobenzenesulfonyl chloride is referred to intermediate in the article

Table 2: Melting points of different samples of sulfathiazole

Acid acceptors	3:1 ratio	1:1 ratio	1:3 ratio
	Melting point observed (°C)		
Pyridine	201**	199	204**
Sodium bicarbonate	195	202**	195
Ammonium hydroxide	189	209	185
Dimethylaniline	208	185	190

This observation was performed for 12 synthesized sulfathiazole samples obtained (with 3:1, 1:1, and 1:3 ratios of intermediate to 2-aminothiazole for different acid acceptors) and best sample were selected **represents best samples compared with standard data

Table 3: Yields of sulfathiazole samples

Acid acceptors	% recovery		
	3:1 (sample 1)	1:1 (sample 2)	1:3 (sample 3)
Pyridine	97.55*	94.56	91.93*
Sodium bicarbonate	94.80	95.71*	89.33
Ammonium hydroxide	92.38	93.06	87.38
Dimethylaniline	94.26	94	88.03

The yields of all the 12 synthesized sulfathiazole samples with 3:1, 1:1, and 1:3 ratios of p-acetamidobenzenesulfonyl chloride to 2-aminothiazole with different acid acceptors are tabulated where *represents best samples

recrystallized and dried. The dried product is weighed and the percent yield is calculated. The yields of all the samples were calculated and tabulated [Table 3]. Based on these findings three best samples (efficient melting at standard temperature and yield) one from each composition is selected (Sample 1, Sample 2, and Sample 3) for further investigation. It was found that out of all samples, pyridine proved to be the best acid acceptor. Therefore, the product obtained from these samples (with pyridine as acid acceptor) is of good quality [Tables 2 and 3].

Determination of the selected samples by FT-IR spectrophotometer

Best three selected samples are, Sample 1: Here, the (3:1 ratio) sample with acid acceptor pyridine gave good recovery (97.55%) and yield (91.814%). Sample 2: Here, the (1:1 ratio) sample with acid acceptor sodium bicarbonate gave good recovery (95.71%) and yield (81.73%). Sample 3: Here, the (1:3 ratio) sample with acid acceptor pyridine gave good recovery (91.93%) and yield (68.9%).

FT-IR for p-acetamidobenzenesulfonyl chloride^[12]

FT-IR spectra of standard p-acetamidobenzenesulfonyl chloride [Figures 4 and 5]

The spectrum is observed for series of samples of concentrations 10, 20, 30, and 40 µg of pure p-acetamidobenzenesulfonyl

Table 4: Calibration data for intermediate

Concentration (µg)	Absorbance (A)
10	0.315
20	0.621
30	0.823
40	0.988

P-acetamidobenzenesulfonyl chloride is referred to intermediate in the article. The FT-IR plots are drawn for wave number versus %transmission which is converted to absorbance and recorded as following

$$A = \log_{10} (1/\%T)$$

$$A = \log_{10} (1/0.24)$$

$$A = \log_{10} (4.116) = 0.621$$

FT-IR: Fourier transform infrared

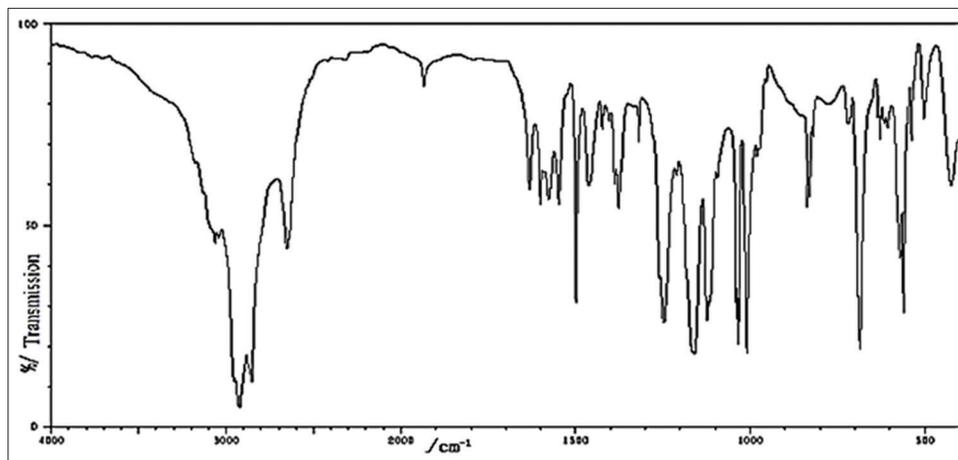


Figure 4: FT-IR Spectra of Standard Intermediate (p-acetamidobenzenesulfonyl chloride). The FT-IR plots are drawn for Wave number vs. %Transmission

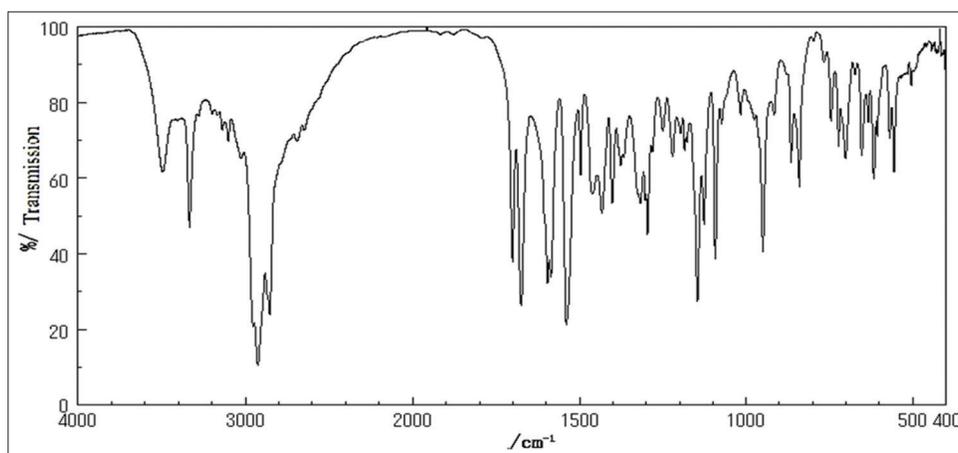


Figure 5: FT-IR spectra of sample (p-acetamidobenzenesulfonyl chloride)

chloride and also the sample. Based on the peaks obtained from FT-IR spectrophotometer, calibration data are generated. The absorbance obtained for a sample at 20 μg is 0.601. The absorbance for standard sample of p-acetamidobenzenesulfonyl chloride at 20 μg is 0.621. It fits the accuracy in Table 4.

Table 5: Calibration data for sulfathiazole

Concentration (μg)	Absorbance (A)
10	0.102
20	0.387
30	0.657
40	0.844

The FT-IR plots are drawn for wave number versus % transmission which is converted to absorbance and recorded, FT-IR: Fourier transform infrared

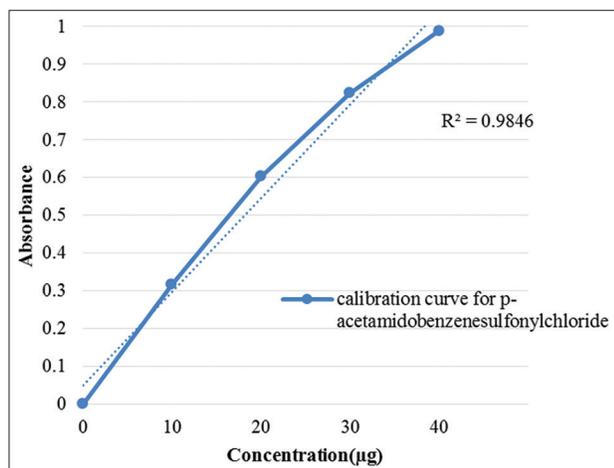


Figure 6: Calibration graph for p-acetamidobenzenesulfonyl chloride. Standard sample is made using Potassium bromide pellets at different concentrations 10 μg , 20 μg , 30 μg and 40 μg and the readings are noted

Calibration graph for p-acetamidobenzenesulfonyl chloride [Figure 6]

FT-IR for Sample 1 (sulfathiazole with 3:1 ratio of intermediate to amine)

FT-IR spectra of standard sulfathiazole [Figure 7]

The spectrum is observed for series of samples of concentrations 10 μg , 20 μg , 30 μg , and 40 μg of standard sulfathiazole, and calibration data was generated. Similarly, the sample is analyzed at wavelength 480 nm for 20 μg sample, where absorbance obtained is 0.365, which is very near to the absorbance for standard sulfathiazole (0.387) [Table 5].

DISCUSSION

The identification test was performed for p-acetamidobenzenesulfonyl chloride (intermediate) and three samples of sulfathiazole. The obtained graphs were compared to standard graphs. Functional groups were identified for all the samples at similar wavelengths to that of standard graphs and structures were identified.

In FT-IR results of p-acetamidobenzenesulfonyl chloride and sulfathiazole, Sample 1 peaks obtained were very close to the standard data and resulted in appropriate structures, whereas in the other samples identified were appropriate but disturbed peaks were observed to a higher extent due to impurities.

The calibration charts were plotted for standard p-acetamidobenzenesulfonyl chloride and sulfathiazole at different concentrations to corresponding absorbance. The absorbance at 20 μg for the standard p-acetamidobenzenesulfonyl chloride and sulfathiazole

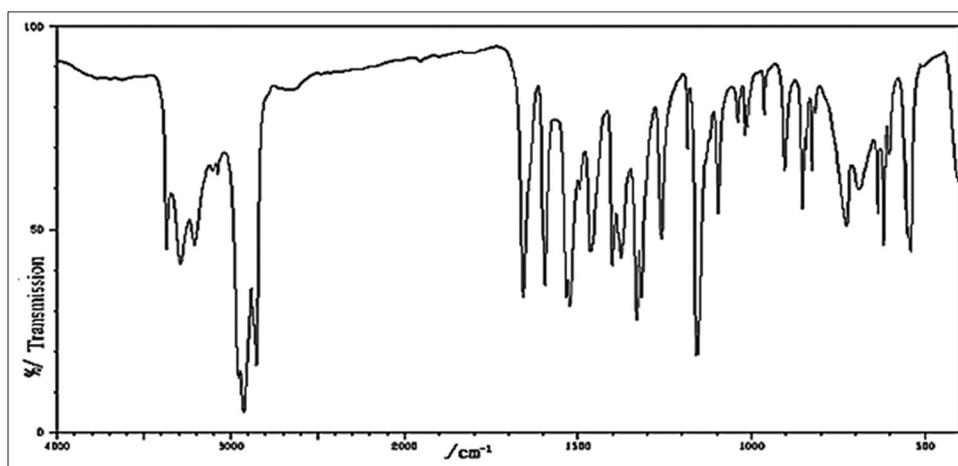


Figure 7: FT-IR spectra of standard sulfathiazole

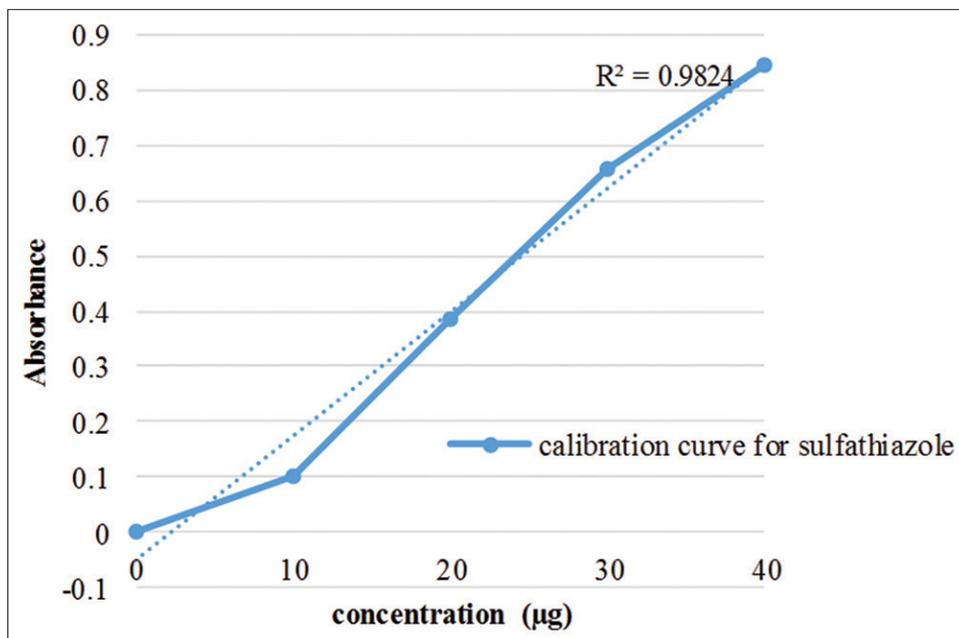


Figure 8: Calibration graph for pure sulfathiazole. Standard sample is made using Potassium bromide pellets at different concentrations 10 µg, 20 µg, 30 µg and 40 µg and the readings are noted.

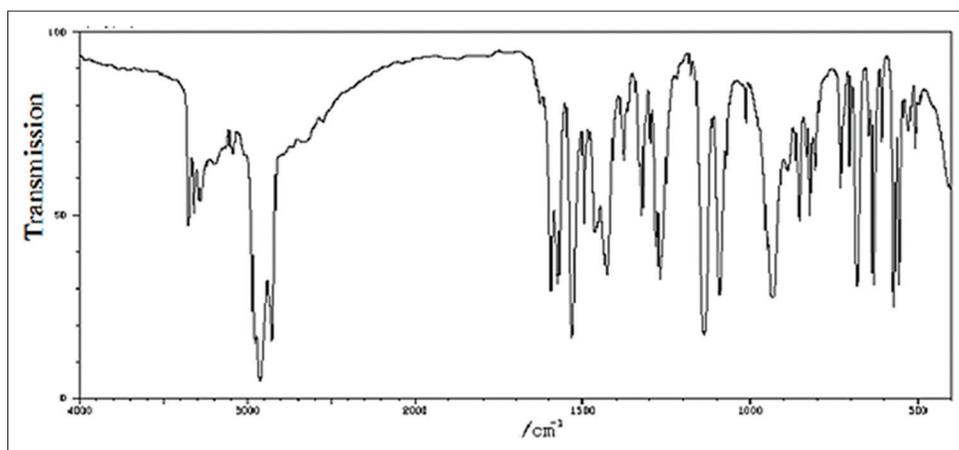


Figure 9: FT-IR for Sample 1 (sulfathiazole with 3:1 ratio of intermediate to amine)

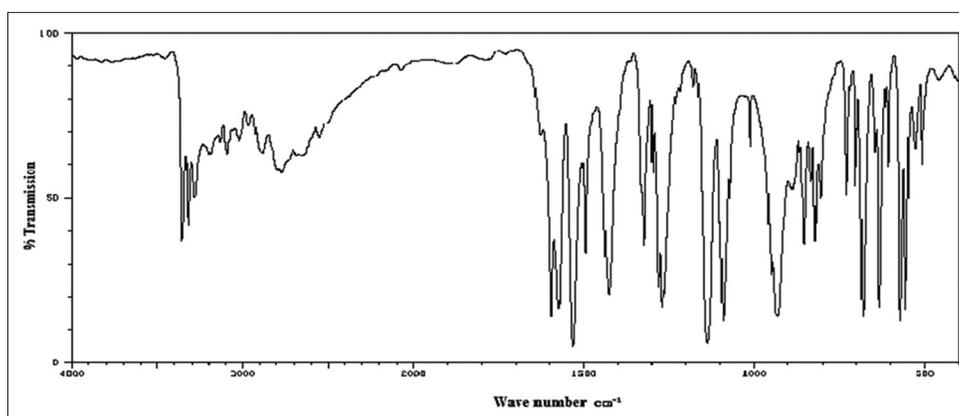


Figure 10: FT-IR for sample 2 (sulfathiazole with 1:1 ratio of intermediate to amine)

was compared to the absorbance at 20 µg for corresponding samples. This resulted in the best quality of p-acetamidobenzenesulfonyl chloride and sulfathiazole Sample 1 (with 3:1 ratio of intermediate to amine) when

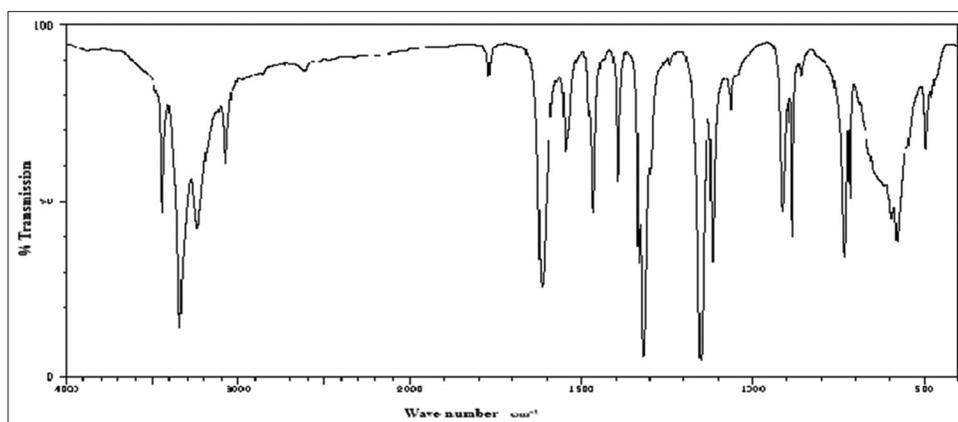


Figure 11: FT-IR for sample 2(sulfathiazole with 1:1 ratio of intermediate to amine)

Table 6: Absorbance observed for pure sulfathiazole and other 3 samples at 20 µg concentration

Concentration of sulfathiazole (µg)	Absorbance (A) of pure sulfathiazole	Absorbance (A) of Sample1	Absorbance (A) of Sample 2	Absorbance (A) of Sample 3
20	0.387	0.365	0.259	0.88

The best samples were selected based on the melting point test and yield

compared to other samples. R^2 plotted for all the graphs showed that the method followed for experimentation gave maximum accuracy and best results [Table 6].

CONCLUSIONS

Among the reaction ratios studied for sulfathiazole, sample with 3:1 ratio of p-acetamidobenzenesulfonyl chloride to 2-aminothiazole with pyridine as an acid acceptor proved to be the best reactant ratio. The process employed for experimentation proved to be an efficient and time-saving process when compared to general processes as reported in the literature. Pyridine is the best acid acceptor as compared to other acid acceptors. Maximum percent yield obtained is 91.34%. FT-IR spectrum is a reliable technique for establishing the identity of sulfathiazole as well as the intermediate.

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