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Development of new methods for Determination of Sulpha Drugs with N-Chlorosacchrin Reagent

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Abstract - Sulpha drugs (sulphanilamide and their derivatives) are widely used as antibacterial drugs. An accurate and rapid method for quantitative determination of sulpha drugs and sulphanilamide would be of great importance. In literature several methods have been discussed for determination of sulphanilamide. The previous methods upon the evaluation of their nitrogen and sulphur contents while the latter were based upon the reaction of functional groups present in them.

Keywords: N-Chlorosaccharin Reagent, Sulpha Drugs, Sulphanilamide, Sulphaguanidine, Sulphacetamide, Sulphonic Acid

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INTRODUCTION

Diazotisation of aromatic amino group has been suggested for determination of sulphanilamides by various groups of workers.[1]

Fischbach[2] suggested a method for determination of sulphanilamide and sulphaguanidine using HCl as solvent, sidium nitrate as titrating reagent and a mixture of potassium bromide and p-dimethylaminobenzaldehyde as indicator. Kekemi[3] et al. detected the end point in diazotisation by externally using a test paper impregnated with 3% dimethylaminobenzaldehyde. El- Sebai[4] et al. used 0.1% methanolic solution of sodium1-(bezylamino)-azobenzene 1-4-sulphonate as indicator.

Butt[5] and Conway[6] determined sulphanilamides from diazotisation by potentiometric titrations.

Yamagishi[7] et al.developed a new geometric method in which diazonium compounds were using potassium nitrite and sulphanilamides and then decomposed, the liberated nitrogen was collected and its volume measured .

These diazotisation methods suffered from the defects that they require cooling in ice bath and nitrous acid is an unstable reagent which requires standardisation.

As the sulphonamide functional groups contains at least one hydrogen atom hence it gives precipitate with silver ion.

On the basis of this reaction, various group of workers[8,9] developed precipitation method using silver nitrate as reagent.

The main limitation of silver nitrate method is that some derivatives of sulphonamides like sulphanilamide, sulphacetamide and sulpha cannot be determined by this method due to low reactivity of hydrogen atoms.

Schulek and Rozsa[10] developed a new method for determination of determination of unsubstituted sulphonamides based on their hydrolysis by heating with dil. H_2SO_4 into free sulphonic acids and ammonium sulphate as:

$$2\text{ -}SO_2NH_2 + H_2SO_4 + 2H_2O \longrightarrow 2\text{ -}SO_3H + (NH_4)_2\,SO_4$$

Then ammonia was steam distilled and titrated against standard acid solution. De Reeder[11] utilised under Kejaldah[12] digestion method for conversion of the substituted sulphonamides to ammonia.

A macro scale procedure to determine sulphonamides based on non- aquous titration of weakly acidic -SO_2NH- gp. using standard solution of sodium methoxide as titrant and methanol or benzene as solvent was developed by Fritz et al.[13]

Ma et al.[15] also adopted this method for micro scale determinations.

Tomicek,[16] Markunas[17] et al. and De Reeder[18] determined sulphanilamide as base by the use of galacial acetic acid as solvent and perchloric acid as titrant. In special cases sample was dissolved in

ethanol and titrated against standard 0.01N hydrochloric acid.

The primary sulphonamide function on treatment with conc. nitric acid yields one equivalent of nitrous oxide in presence of sulphuric acid or hydrochloric acid.

$$-SO_2NH_2 + HNO_3 + H_2O \longrightarrow -SO_3H + NH_4NO_3$$

$$NH_4NO_3 \longrightarrow N_2O + 2H_2O$$

Gaind and Punn[21] determined aminobenzene sulphonamides by acetylation using acetic anhydride and Pyridine as reagents.

Jindu and Sipos[22] used hydrolysis method followed by ion exchange method to analyse sulphanilamides (sulpha drugs). Hydrolysis was carried out with 1N HCl in a sealed tube at 100 - 200^{0}C and the reaction products chromatographed over cationic exchanger resins. The eluate containing sulphanilic acid was titrated potentiometrically against standard sodium hydroxide solution.

Tiwari[23] et al. also used ion exchange method for micro scale determination of sulpha drugs.

The colourimetric methods reported for determination of sulphanilamides depends on the reaction of aromatic amino group present in these compounds. Brattan[24] et al. proposed colourimetric methods for determination of sulphanilamides based diazotisation of aromatic amino group followed coupling with N-(1-napthyl) ethylene diamine producing intense colour. Werner[26] had developed colourimetric method in which p-dimethylamino benzaldehyde was reacted with sulpha drugs to produce yellow anils. The optical density of the coloured solution in each case was measured photometrically.

Kegawa[27] studied coloured reaction of certain drugs with o-diacetylbenzene as an analytical reagent.

Stewart and Wilkin[28] used quenching fluorometry of 9-chloroacidine for determination of sulpha drugs.

Shafer and Wilde[29] suggested the determination of sulphonic acid amide by thermometric titrations by the use of hypochlorite.

Doneyal and Somon[30] gave a direct titrimetric method by mixing the sample in glacial acetic acid and used bromine as titrant in same solvent.

Barakat and Monier[31] used N-Chlorosucinimide as reagent and methyl red as indicator for direct titrimetric determination of sulphanilamide,sulphacetamide and sulphaguanidine .

Sharma[32] et al. used bromine monochloride for indirect titration whereas Pande et al. N-Chlorosucinimide as reagent and neutral red as indicator for direct titrimetric method for determination of sulpha drugs.

PRESENT WORK

The present study was undertaken with a view to know the possibility of using N-chlorosaccharin reagent for determination of sulpha drugs and the results of determination are incorporated in this chapter.

METHODOLOGY

Before using the reaction for reaction for quantitative determination of sulpha drugs, stoichiometry of reaction was determined in each case. An accurately weighed amount of 40-100 mg of compound was dissolved in 100 ml of 4N HCl to prepare stock solutions of sulpha drugs. Aliquots containing 1-5 mg of samples were taken in 100 ml glass stoppered conical flask follwed by the addition of two drops of methyl orange (0.04%) as indicator. The solutions were titrated against standard 0.02M N-chlorosaccharin solution dropwise with shaking thoroughly after each addition till the disappearance of pink colour of indicator. A blank experiment was also carried out without samples under the identical experimental conditions. The results of stoichiometry of all the determinations using N-chlorosaccharin are in agreement with the corresponding results obtained by using N-Chlorosucinimide. The obtined results clearly indicate that the reaction of N-chlorosaccharin with sulpha drugs is complete and stoichiometric.

RESULTS AND DISCUSSIONS

SMALL SCALE (MILIGRAM LEVEL) DETERMINATION OF SULPHA DRUGS

With the recommended procedures the small scale that is miligram level determination of sulpha drugs like sulphanilamide, sulphapyridine, sulphaguanidine, sulphadiazine and sulphamerazin was achieved.

SMALL SCALE DETERMINATION OF SULPHANILAMIDE USING N-CHLOROSACCHARIN

Aliquots taken (ml)	Amount taken (ml)	Stoichiometry	Amount Recovered (mg)	Error (%)
1.000	1.200	2	1.209	+0.50
1.000	1.200	2	1.196	-0.33
1.000	1.200	2	1.195	-0.41
2.000	2.400	2	2.390	-0.41
2.000	2.400	2	2.393	-0.29
2.000	2.400	2	2.408	+0.33
3.000	3.600	2	3.620	+0.55
3.000	3.600	2	3.580	-0.55
3.000	3.600	2	3.610	0.27
4.000	4.800	2	4.820	+0.41
4.000	4.800	2	4.810	+0.21
4.000	4.800	2	4.870	-0.21

SMALL SCALE DETERMINATION OF SULPHAGUANIDINE N-CHLOROSACCHARIN

Aliquots taken (ml)	Amount taken (ml)	Stoichiometry	Amount Recovered (mg)	Error (%)
1.000	1.300	2	1.294	+0.46
1.000	1.300	2	1.305	+0.38
1.000	1.300	2	1.293	-0.53
2.000	2.600	2	2.612	+0.46
2.000	2.600	2	2.610	+0.38
2.000	2.600	2	2.590	-0.38
3.000	3.900	2	3.919	+0.48
3.000	3.900	2	3.916	+0.48
3.000	3.900	2	3.890	-0.25
4.000	5.200	2	5.220	+0.38
4.000	5.200	2	5.178	-0.42
4.000	5.200	2	5.223	+0.44

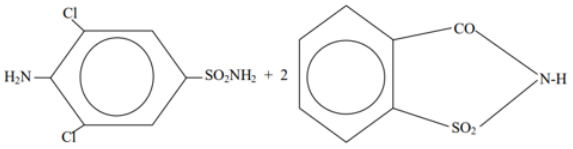
SMALL SCALE DETERMINATION OF SULPHAPYRIDINE USING

N-CHLOROSACCHARIN

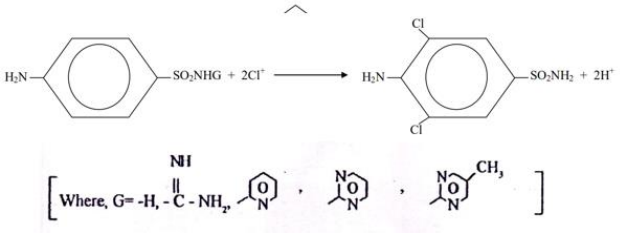
Aliquots taken (ml)	Amount taken (ml)	Stoichiometry	Amount Recovered (mg)	Error (%)
1.000	1.150	2	1.145	-0.43
1.000	1.150	2	1.144	-0.52
1.000	1.150	2	1.153	+0.26
2.000	2.300	2	2.290	-0.43
2.000	2.300	2	2.291	-0.39
2.000	2.300	2	2.312	+0.52
3.000	3.450	2	3.441	-0.26
3.000	3.450	2	3.442	-0.23
3.000	3.450	2	3.461	+0.31
4.000	4.600	2	4.620	+0.43
4.000	4.600	2	4.619	+0.41
4.000	4.600	2	4.590	-0.19

The description of determination of sulpha drugs by general procedure as discussed in experimental part of this chapter have been given in table II. From analysis of results, it is clear that the relative error does not exceed ±1.90%. The results obtained by using N-chlorosaccharin are comparable with those obtained earlier by using N-Chlorosucinimide.

To know about the reactions involved and also to understand the reaction conditions sulphanilamide was chosen as representative compound. Better results were obtained in direct titrimetric method using methyl red as indicator. The product of reaction was isolated and identified as 4-Amino-3,5-dichlorobenzene sulphonamide (m.p. 226^{0}C). 4-Amino-3,5-dichlorobenzene sulphonamide was also prepared by direct chlorination of sulphanilamide. The melting point of both were identical. The observed stoichiometry of second may also be explained by assuming the formation of dichloro derivatives as:



The presence of amino group in benzene nucleus of sulpha drugs (sulphanilamide) increases the activity of ortho and para positions of benzene ring but the para position of such compound is already occupied by sulphonic acid amide group hence only the two ortho positions remains activated and takes two chlorine atoms to form a dichloro derivatives as given below :



It is reported that -SO_3H and -COOH groups present at ortho or para positions with respect to amino or hydroxyl groups in aromatic amines or phenoles are replaced by Cl^+. But in case of sulphanilamides no such replacement takes place. The reason is that, less basic group is better leaving group. Therefore -SO_3H gp. is more acidic and less basic as compared to -SO_2NH_2 gp. which is less acidic and more basic and hence it undergoes easy replacement. Moreover, Cl^+ remains in contact with sulphanilamides only for a definite time intervel during direct titration.

The observed stoichiometry and mechanism are in agreement with those proposed by Pande et al. using N-chlorosuccinimide.

ADVANTAGES

This procedure gives more accurate results with all the sulpha drugs studied. There is no requirement of any drastic reaction condition like hydrolysis and cooling of reaction mixture. The results obtained are more or less in agreement with those obtained earlier by the use of N-Chlorosucinimide. Therefore N-chlorosaccharin is a suitable substitute of N-Chlorosucinimide for determination of sulpha drugs.

EXPERIMENTAL CONDITIONS:

REAGENTS AND SOLUTIONS

N-CHLOROSACCHRIN; 0.02 M

0.0174 g of N-chlorosaccharin was accurately weighed and dissolved in 40 ml of glacial acetic acid by shaking thoroughly in a 100 ml volumetric flask. The solution was made upto the mark with distilled water and standardised iodiometrically.

SAMPLE SOLUTIONS

40 to 100 ml of sulpha drugs was accurately weighed and dissolved in 100 ml of 4N HCl in a 100 ml volumetric flask.

All the samples were of Baker analysed reagent and their purity was tested by melting point determinations

Hydrochloric Acid; 4N:

Hydrochloric acid was diluted to provide the required concentration.

Glacial Acetic Acid (A.R., B.D.H.):

Methyl Red

0.04% w/v aquous solutions of methyl red was used as indicator.

General Procedure:

An aliquot containing 1-5 mg of samples were taken in a 100 ml stoppered glass conical flask follwed by addition of two drops of methyl red as indicator solution. The flsk was shaken finely and the reaction mixture titrated against standard solution of N-chlorosaccharin till the disappearance of pink colour of indicator.

A blank experiment was also performed without sample under identical experimental conditions.

Formula for Calculation:

The recovery of sulpha drugs was calculated by the given formula as:

Recovery in mg = $\frac{(V_S - V_B) \times M \times C}{434}$

Where,

V_S = Volume of N-chlorosaccharin solution required to titrate sample (ml).

V_B = Volume of N-chlorosaccharin solution required to titrate blank (ml).

M = Molecular weight of sample.

C = Concentration of N-chlorosaccharin solution in gm/litre.

CONCLUSION

This chapter presents a direct titrimetric method for milligram level determination of sulpha drugs by the use of N-chlorosaccharin reagent and methyl red as indicator.

In this procedure aliquotes containing 2-10 mg of sample (sulpha drug) and 2 drops of methyl red (0.04%) solution are titrated against standard N-chlorosaccharin solution till the disappearance of pink colour of indicator. The stoichiometry of reaction has been determined in each case and the reaction products isolated and identified in case of sulphanilamide. The mechanism of reaction has been proposed on the basis of observed stoichiometry and isolated chloro derivatives. Sulpha drugs are studied and undergo quantitative chlorination on treatment with N-chlorosaccharin yielding dichloro derivatives.

The results of determination in case of sulphaguanidine, sulphanilamide, sulphapyridine and sulphamerazine are tabulated and discussed in detail in this chapter. The errors do not exceed ±1.9%. The results obtained by the use of N-chlorosaccharin (NCSA) are comparable with those obtained earlier using N-Chlorosucinimide (NCS).

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