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Micro Determination of Some Diuretic Drugs along with its Pharmacological Activity

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Abstract:*The development of Diuretic Drugs is used for the increased production of urine. Commonly known as "water pills," these drugs help your kidneys get rid of extra water and salt from your body through your pee. Because you have less total fluid in your blood vessels, like a garden hose that's not turned on all the way, the pressure inside will be lower. This also makes it easier for your heart to pump. On the basis of oxidation pattern and literature available a possible course of reaction for the preparation of Diuretic Drugs such as Diamox (Tab), synomax (Tab), Tebemid (Tab), Frusemene (Tab), Aquazide (Tab), Xenia (Tab), Kratol (Inj), Mannigyl (Inj), Aldactide (Tab) and spilactone (Tab) are discussed.*

Background*: Diuretics refer to substances that cause loss or removal of excess water from the body in the form of urine. The specific medicines that act as diuretics which are generally referred as the "water pills". Vegetables like asparagus,tomatoes and oats etc. are certain natural diuretic. Since the discovery of thiazide diuretic in 1957, which for the first time offered the possibility of efficiently reducing blood pressure. These drugs have represented a fundamental tool for the treatment of hypertension. Moreover, placebo controlled clinical studies have documented clearly the benefit of thiazide diuretics, either given alone or combined with blockers, in reducing cardiovascular morbidity and mortality.*

Materials and Methods*: 1-5mg of the sample were taken in 100mL stoppered conical flask followed by the addition of 5mL AHC (0.1M) reagent, prepared in 0.5N--HNO3 . The reaction mixture was Introduction Rajeev Singh Baghel : 114 shaken well and allowed to react for required reaction time at room temperature (25-30ºC). The unconsumed Ce(IV) was titrated against 0.025M FAS solution using two drops fo ferroin indicator (0.001M). A blank experiment was also performed under identical conditions using all the reagents except the sample. The amount of AHC consumed for the sample was calculated with the difference in the titre values of ferrous ammonium sulphate solution for blank and actual experiments. The recovery of the sample was calculated with the amount of AHC consumed for the sample. For every sample percentage error, coefficient of variation and standard deviation were calculated.*

Results*: The development of Diuretic Drugs is used for the increased production of urine. Commonly known as "water pills," these drugs help your kidneys get rid of extra water and salt from your body through your pee. Because you have less total fluid in your blood vessels, like a garden hose that's not turned on all the way, the pressure inside will be lower. This also makes it easier for your heart to pump. On the basis of oxidation pattern and literature available a possible course of reaction for the preparation of Diuretic Drugs such as Diamox (Tab), synomax (Tab), Tebemid (Tab), Frusemene (Tab), Aquazide (Tab), Xenia (Tab), Kratol (Inj), Mannigyl (Inj), Aldactide (Tab) and spilactone (Tab) are discussed.*

Conclusion:*The development of Diuretic Drugs is used for the increased production of urine. Commonly known as "water pills," these drugs help your kidneys get rid of extra water and salt from your body through your pee. Because you have less total fluid in your blood vessels, like a garden hose that's not turned on all the way, the pressure inside will be lower. This also makes it easier for your heart to pump. On the basis of oxidation pattern and literature available a possible course of reaction for the preparation of Diuretic Drugs such as Diamox (Tab), synomax (Tab), Tebemid (Tab), Frusemene (Tab), Aquazide (Tab), Xenia (Tab), Kratol (Inj), Mannigyl (Inj), Aldactide (Tab) and spilactone (Tab) are discussed.*

Key Word*: Micro Determination, Diuretic Drugs, Pharmacological Activity*

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I. Introduction

Diuretics refer to substances that cause loss or removal of excess water from the body in the form of urine. The specific medicines that act as diuretics which are generally referred as the "water pills". Vegetables like asparagus,

tomatoes and oats etc. are certain natural diuretic. Since the discovery of thiazide diuretic in 1957, which for the first time offered the possibility of efficiently reducing blood pressure. These drugs have represented a

fundamental tool for the treatment of hypertension. Moreover, placebo controlled clinical studies have documented clearly the benefit of thiazide diuretics, either given alone or combined with blockers, in reducing cardiovascular morbidity and mortality. Diuretics are used for many reasons. They may be indicated for people who suffer from edema an intense

accumulation of fluids in the body tissues and those who suffer from high blood pressure or other heart related diseases. Increasing the production of urine not only releases fluid, but helps rid the body of excess salts and may reduce blood volume. Other uses of diuretics are to treat heart failure, liver cirrhosis, hypertension and certain kidney diseases. Some diuretics such as acetzolamide help to make the urine more alkaline and are helpful in increasing excretion of substances such as Aspirin in case of overdose or poisoning. diuretics are often abused by sufferers of eating disorders, especially bulimics in attempts at weight loss. The side effects of water pills depend on the type being used and the presence of other medical conditions such as kidney and heart disease. Although most of the side effects of water pills are mild and temporary.

Although a long list of diuretics are available but I have restricted myself to only some of these important drugs i.e. Acetazolamide, Furosemide, Hydrochlorothiazide, Mannitol and spironolactone. As described in the survey of literature, the AHC reagent has not been used for the estimation of diuretic drugs. Therefore in the present chapter, I have described a simple method for the determination of above diuretics in pure form an in their pharmaceutical preparations such as Diamox (Tab), synomax (Tab), Tebemid (Tab), Frusemene (Tab), Aquazide (Tab), Xenia (Tab), Kratol (Inj), Mannigyl (Inj), Aldactide (Tab) and spilactone (Tab).

II. Material and Methods

For testing the quantitative validity of reaction, Acetazolamide was taken as test sample. Different amount of sample (1-5mg) were allowed to react with varying concentrations of ammonium hexanitrato cerate (IV) at room temperature (25-30ºC) for different intervals of time. The unconsumed AHC was back titrate cerimetrically. A blank

experiment was also run under identical conditions using all the reagents except the sample. The difference in the titre values of ferrous ammonium sulphate consumed for blank and actual experiments was used to calculate the amount of the sample present in a particular experiment. The stoichiometry of the reaction was established for each sample and a possible course of reaction was also suggested. On the basis of the reaction conditions developed for Acetazolamide the determination of other compounds in the pure form and in their pharmaceutical preparations were done.

III. Resultand Discussion

In order to develop suitable reaction condition for the determination of above diuretics with AHC reagent, the effect of different variables was studied.

Keeping the amount of Acetazolamide and concentration of AHC reagent as constant, the reaction time was varied from 1-25 minutes. aliquots containing 5 mg of Acetazolamide were taken in 100mL stoppered conical flask and 5mL of 0.1M AHC reagent prepared and 10mL of 4Msulphuric acid was added to it. Now the reaction mixture was shaken well and allowed to react at room temperature for 1-25 minutes. After the reaction was over the unconsumed AHC was determined by back titrating the reaction mixture against standardized ferrous ammonium sulphate (0.025M) solution using ferroin as indictor. The percentage recovery of the sample does not change after a proper reaction time. Therefore, further estimation was done on the same reaction time (Table-3). similar experiments were performed with other samples as well. It was observed that Acetazolamide and Mannitol requires 5 minutes to complete the reaction but furosemide, hydrochlorothiazide and spironolactone takes 15 minutes to complete the reaction.

Keeping the reaction time, amount of Acetazolamide and concentration of AHC (0.1M) constant, the concentration of sulphuric acid was varied from (1-7M) and the results were noted in (Table-8). Results given in the table shows that the best recovery of the samples was obtained at 4M concentration of sulphuric acid. To ascertain the exact amount of 4Msulphuric acid needed for the reaction, some variations in the volume were done (Table-9), accurate results were obtained at 10mL of the acid. Similar results were obtained in case of other diuretics.

Thus, for completing the reaction and getting accurate results 10mL of 4 msulphuric acid was recommended for the experiment.

Keeping the reaction time, amount of Acetazolamide and concentration of sulphuric acid as constant, the effect of varying concentration of AHC was studied. 5 mg of the sample was allowed to react with 5 mL of varying concentration (0.01- 0.1M) of AHC. The unconsumed AHC was back titrated with FAS (0.025M) solution using ferroin indicator and the recovery of the sample was calculated. It was found that the best results were obtained at 0.1M concentration of AHC. The concentration of reagent less than 0.1M gives higher percentage of error and low recovery (table-10). The reason for this is due to incomplete reaction of the reagent with the sample. the higher concentration than 0.1M gives no significant advantage in percentage recovery.

therefore, the higher concentration of the reagent was avoided. variation in the volume of 0.1M AHC was also studied (Table-11). It was observed that 5mL of 0.1M AHC gives accurate result. Thus, for completing the reaction, getting accurate results and also avoiding the wastage of the reagent, 5mL of 0.1M AHC was recommended for the experiment. In the similar way the studies of different variables were also done with Acetazolamide.

Keeping all other conditions constant, the reaction temperature was varied from 5ºC onwards and the recovery of Acetazolamide was calculated. It was observed that the reaction was completed within 15 minutes at room temperature (25-30ºC). The heating of the reaction mixture directly in flame, hot plate or boiling water bath gives inaccurate results. It may be due to decomposition of reagentat high temperature.

Table-1: Determination of stoichiometry of Acetazolamidewith 0.1M ammonium hexanitrato cerate (AHC) reagent inacidic medium)

S. N.	Aliquots taken (mL)	Amount present* (mg)	Reaction time (min.)	Titre value of ferrous ammonium Sulphate with sample	No. of moles of AHC with per mole of Acetazolamide
1	2.00	1.974	2	14.42	1.388
2	2.00	1.974	5	14.24	1.448
3	2.00	1.974	7	14.06	1.642
4	2.00	1.974	10	13.88	1.986
5	2.00	1.974	15	13.88	1.986
6	2.00	1.974	20	13.88	1.986
7	2.00	1.974	25	13.88	1.986

* In each case three determinations were done

Although the reaction is competed at room temperature. But the experiment was also carried out at lower temperature up to 5ºC. In this case also a decrease in recovery of the sample was noted. It shows that the reaction is slow at lower temperature. Thus, for the estimation of Acetazolamide a reaction temperature of 25-30ºC was maintained. Such experiments were carried out with all other samples and the recovery was noted. It was observed that the reaction recommended temperature was suitable for all other diuretics e.g., Furosemide, Hydrochlorothiazide, Mannitol and spironolactone.

The stoichiometry of the reaction for Acetazolamide was established in the following way: 1-5 mg of the sample was taken in a 100mL stoppered conical flask and 5mL of 0.1M reagent, prepared in 0.5N nitric acid was added. The reaction mixture was shaken thoroughly and allowed to react for required reaction time at room temperature (25-30ºC) and then added 10mL of 4MH2SO4 solution. The ferroin indicator (0.001M). A blank experiment was also run under identical conditions using all the reagents except the sample. Number of moles of the AHC consumed for Acetazolamide was calculated with the difference in the titre values of FAS solution consumed for blank and actual experiments (Table-1). Similar experiments were performed for Furosemide, Hydrochlorothiazide, Mannitol and Spironolactone. It was observed that the molar ratio of above drugs with AHC reagent was 1:2, 1:4, 1:2 and 1:4 respectively.

To evaluate the authenticity of the method recovery experiments were also carried out by standard drug addition method. For such experiments a known amount of the pure drug was taken and varying amounts of the pharmaceutical preparations of that compound was added. The total amount present in the sample was find out by usual method.

The stoichiometric ratio between AHC reagent andDiuretics such as Acetazolam ide (1:2), Furosemide (1:2),Hydrochlorothiazide (1:4), Mannitol (1:2) and Spironolactone (1:4)has already been mentioned (Table-2) in pure form and in theirpharmaceutical preparations. This ratio remains constant evenunder varying reaction conditions. It has been observed in theexperiments on variation of reaction time (table-3), that aparticular reaction time is needed for completion of the reaction,concordant and accurate results. The reaction time varies

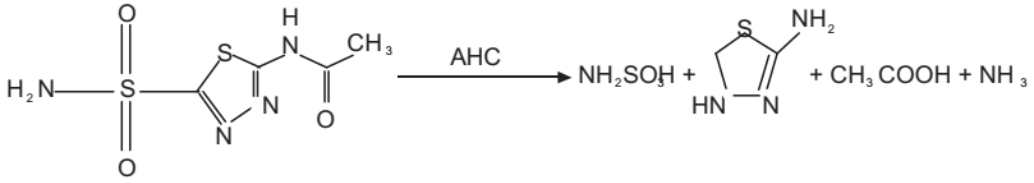
fromone compound to another. At the reaction time lesser than thedescribed (table-3), inaccurate results are obtained because ofincomplete reaction. An increase in the prescribed reaction timedoes not give any effect in the efficiency of the results.

The use of H2SO4 as a proper reaction medium hasalso been studied. H2SO4 gives quantitative and stoichiometric

results with Acetazolamide and Furosemide. The same resultswere obtained in the case of other samples. Reaction was alsocarried out in the absence of H2SO4 . In this case, it was foundthat the reaction is slow and the percentage of error is veryhigh. So, it was observed that a proper reaction medium isnecessary for the accurate results. After variation in theconcentration and volume of H2SO4 , it was observed that theuse of 10 mL of 4MH2SO4 was necessary for suitable reactionmedium.

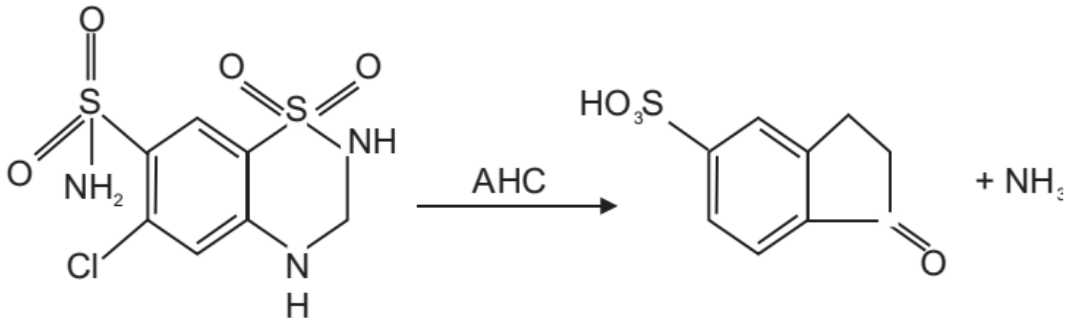
AHC is the main active agent, which reacts withdiuretic drugs. As indicated in the (table-11), that 5mL of 0.1MAHC was sufficient for all the samples for accurate results.Reaction was also carried out at lower and higher (0.01-0.1M)concentration at variable volume of AHC. In this case, it wasobserved that the concentration and volume than the prescribedunder reaction conditions gives low recovery because ofinsufficient reagents. Higher concentration and volume does notgive any improvement over the results. Therefore prescribedconcentration and volume of the AHC reagent was used. Theeffect of temperature has also been studied. It is observed thatthe results improve with increase in reaction temperature. Thebest recovery was obtained at room temperature (25-30ºC). Anincrease in the reaction temperature above gives inaccurateresults (table-12). At a lower temperature (25-5ºC), it is
decreased that the reaction is very slow and needs morereaction time. It gives higher percentage of error.

Possible course of reaction is as follows. The survey of literature shows that the diureticshave largely been studied by different oxidizing agents.Acetazolamide is a substituted derivative of thiazide on thenitrogen of acetamide. It is a derivative of thioheterocycliccompounds having two nitrogen at 3, 4-positions. At position2 is acetamide attached through nitrogen and position 5 is asulphonyl group. the heterocyclic structure is fairly stable anddoes not get reacted under these mild conditions. The possibilityis that the acetamide side chain gets hydrolyzed liberating acetic acid and an amino group remains at position 2. Similarlythe sulponyl group gets oxidized to corresponding sulphonic acidliberating NH3 gas. On the basis it can be proposed thatfollowing reaction products are obtained under the presentreaction conditions.

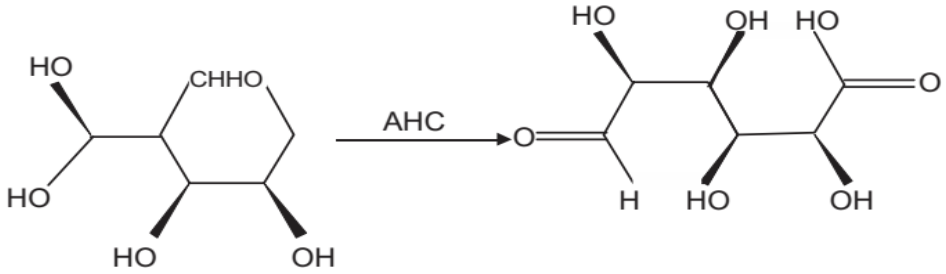


Furosemide is a derivative of anthranilic acid. Atpara position to amino group and sulphamoyl group is attached while meta position there is a chlorine atom. the amino groupof the acid is substituted by furfuryl group. which is a oxygencontaining heterocyclic compound. the present reagent is worksas mild hydrolyzing as well as oxidizing reagent looking at thecomplete structure and the stoichiometric ration of the reagentit is proposed that the sulphamoyl group gets converted toSO3H group, liberating NH3, while the furfuryl group isconverted to furfulal.

The next compound is Hydrochlorothiazide hashighly complex structure having functional groups at differentpositions. Since it is derivative of sulphonamide. It can bethought that the active compound may get converted tocorresponding to sulphonic acid group. Only the position 3 isa CH2 group which is under strain due to presence of twonitrogen. Therefore, it is possible at this position will be oxidizeto keto group. In this way the final reaction product is proposedbelow:



The oxidation of Mannitol has already been studiedwith sodium periodate in acidic solution iodometrically. It isreported that the polyhydric alcohols like Mannitol are oxidizedin the following way. One mole of the reagent is consumed andthe oxidation of terminal CH2OH group to HCHO group andCHOH groups to formic acid is reported.On the basis of above reaction Mannitol givesfollowing oxidation reaction with AHC.



IV. Conclusion

The development of Diuretic Drugs is used for the increased production of urine. Commonly known as "water pills," these drugs help your kidneys get rid of extra water and salt from your body through your pee. Because you have less total fluid in your blood vessels, like a garden hose that's not turned on all the way, the pressure inside will be lower. This also makes it easier for your heart to pump.On the basis of oxidation pattern and literature available a possible course of reaction for the preparation of Diuretic Drugs such as Diamox(Tab), synomax (Tab), Tebemid (Tab), Frusemene (Tab), Aquazide(Tab), Xenia (Tab), Kratol (Inj), Mannigyl (Inj), Aldactide (Tab)and spilactone (Tab) are discussed.

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