Pharmaceutical Analytical Chemistry I

الأستاذ الدكتور جمعه الزهوري (دكتوراه صيدلة-ألمانيا 1991)

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REDOX titration of Drugs

A volumetric method of Drugs analysis which relies on oxidation or reduction of the analyte.

Oxidation

Reduction form (Red) ⇌ **Oxidation Form (A_{ox}) + n e^-**

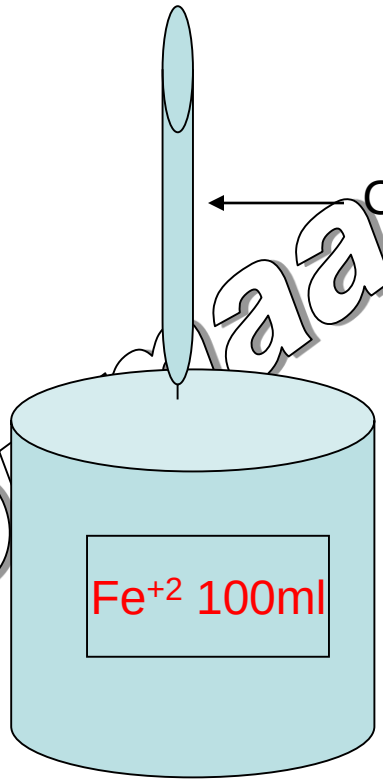
Reducing agent — Reduction — Oxidizing agent

A reducing agent is an electron donor.

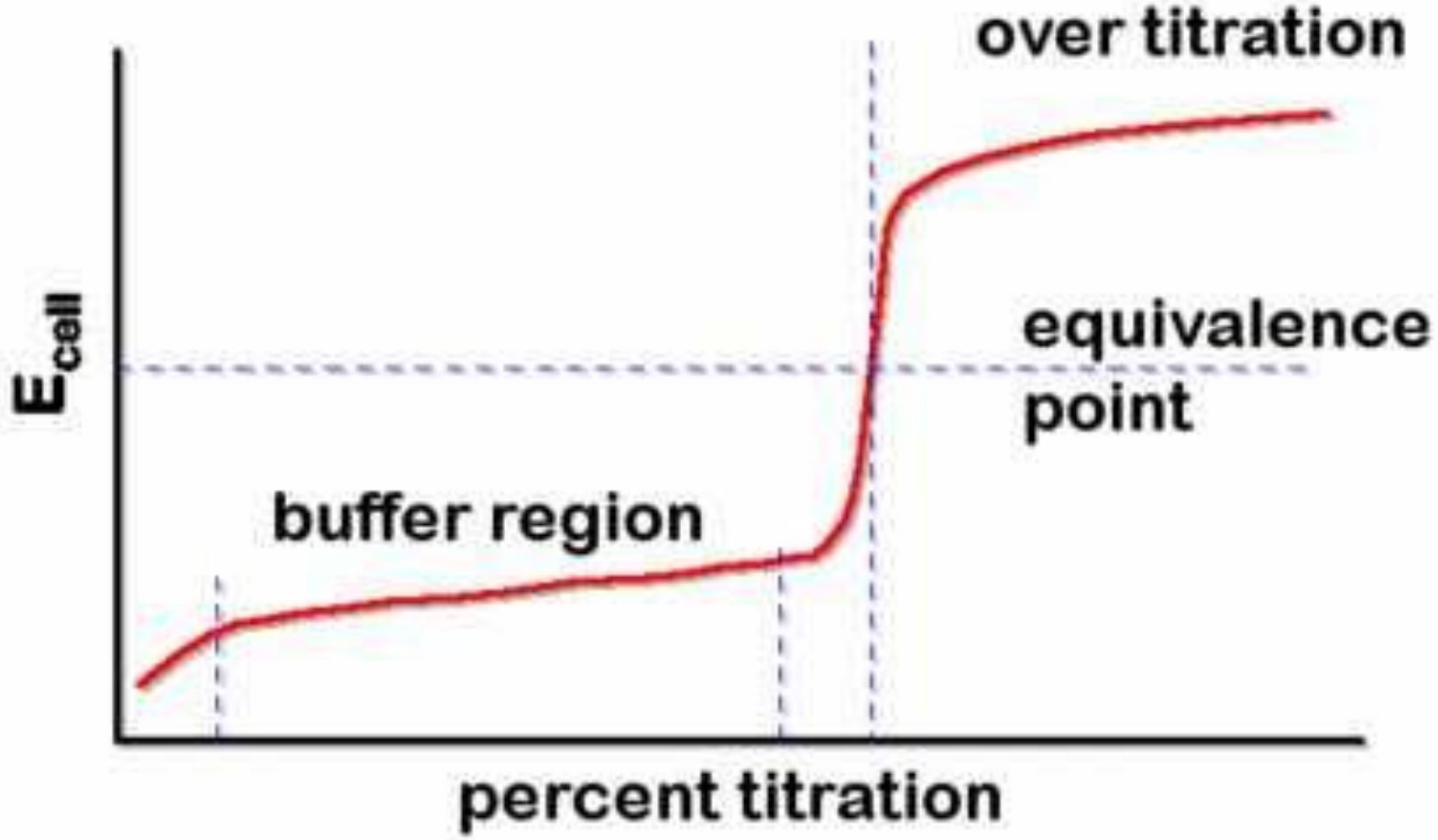
An Oxidizing agent is an electron acceptor

- **half-reaction**
- **Redox couple**

Titration of Fe^{+2} with Ce^{+4}



Titration curves



Redox Titration

Method	St. solution	n	indicator	uses
Manganometry	$KMnO_4$	In acidic = 5	-	H_2O_2 …
Dichromatometry	$K_2Cr_2O_7$	6	Diphenylamine	Fe….
Brom(at)ometry	$KBrO_3$	6	Methyl orange	Isoniazid,Methyl-4-hydroxybenzoat,Propyl-4-hydroxybenzoate,Thymol…
Iodometry And Iodimetry	$I_2(KIO_3+KI)$ Oxidation $KI(Na_2S_2O_3)$ Reduction	1	Iodine/starch	Ascorbic acid, Novalgen, Cephaloridin….
Cerimetry	$Ce(SO_4)_2$	1	Ferroin	Paracetamol , Ferrous Sulphate

Common titrants

Oxidizing titrants

MnO_4^- $E^o = 1.51$ V **Strong Oxidizing agent**

Solutions must be standardized - typically use $Na_2C_2O_4$ (a primary standard material.)

Reagent slowly degrades and MnO_2 must be removed **(Self Indicator , MnO_4^- (violet) Mn^{+2} (colorless)**

No indicator is needed - excess reagent produces a pink solution.

$$MnO_4^- + 8H^+ + 5\,e \longleftrightarrow Mn^{+2} + 4H_2O$$

Potassium Permanganate

- In Acidic media

$MnO_4^- + 8H^+ + 5e^- \longrightarrow Mn^{+2} + 4H_2O$ $\quad E_o = 1.52\ V$

n=5

- In Neutral media

$MnO_4^- + 4H^+ + 3e^- \longrightarrow MnO_2 + 4OH^-$ $\quad E_o = 1.68\ V$

n=3

- In alkali media

$MnO_4^- + e^- \longrightarrow MnO_4^{-2}$ $\quad E_o = 0.54\ V$

n=1

Standardization with sodium oxalate

$MnO_4^- + 8H^+ + 5e^- \longrightarrow Mn^{+2} + 4H_2O$ **.2**

$Cr_2O_4^{-2} \longrightarrow 2CO_2 + 2e^-$ **.5**

$2MnO_4^- + 5C_2O_4^{-2} + 16H^+ \longrightarrow$

$2Mn^{+2} + 10CO_2 + 8H_2O$

Potassium Permanganate Titration

- The dominated media is acidic
- We use sulfuric or phosphoric acid.
- We can not use Hydrochloric acid. $C\,l^- \longrightarrow Cl^0 \uparrow$
- We can not use nitric acid else. Contain small amount of HNO_2
- We don't need external indicator
- Pot .Permanganate solution is not stable and should always standardize.
- $2MnO_4^- + 5H_2O_2 + 6H^+ \longrightarrow 2Mn^{+2} + 2O_2 \uparrow + H_2O$

أمثلة على مقياس البرمنغنات :

1- معايرة كبريتات الحديدي : حيث تؤكسد البرمنغنات الحديد الثنائي إلى حديد ثلاثي بوسط من حمض الكبريت ولايجوز استخدام حمض كلور الماء وتتم المعايرة من دون مشعر خارجي .

2- معايرة الماء الأكسجيني : وتتم أيضاً بوجود حمض الكبريت وتحدد القوة الأكسجينية للماء الأكسجيني بأنها : عدد الميلليليترات من الأكسجين التي يمكن الحصول عليها عندما يتفكك امل من الماء الأكسجيني .

3- معايرة لاكتات الكالسيوم : وتتم من خلال الترسيب على شكل حماضات بوسط حمضي وبوجود حماضات الأمونيوم حيث يفصل الراسب بالترشيح ثم يحرر حمض الحماض ويعاير بالبرمنغنات .

Common titrants

Potassium dichromate $K_2Cr_2O_7$

Oxidizing titrants

$Cr_2O_7^{2-} + 14H^+ + 6e^- \longrightarrow 2\,Cr^{+3} + 7H_2O$ $\quad E^o = 1.33V$

Primary standard material

Less Oxidizing agent than $KMnO_4$

Need an indicator such as diphenylamine sulfonic acid.

Very stable solutions. If air is kept out, it can last for years.

E = 1.44 V

معايرة الغليسيرين :

يتأكسد الغليسيرين بوجود فائض من الكرومات بوسط حمضي شديد ثم يعاير الفائض من الكرومات بعد اضافة يودور البوتاسيوم حيث يتحرر اليود الذي يعاير بثيوت كبريتيت الصوديوم .

Iodimetry & Iodometry

- **Iodine** I_2
- **Iodide** I^-
- **Hypoiodate** IO^-
- **Iodate** IO_3^-
- **Peroidate** IO_4^-

Iodimetry (I_2) اليود هنا مؤكسد

المادة التي تعاير هي مادة مرجعة

- Titrations with I_2 are called iodimetric methods.
- In Iodimetry, the titrant is I_2 and the analyte is a reducing agent. The end point is detected by the appearance of the blue starch iodine color

يستخدم أحياناً الكلوروفورم أو رابع كلور الفحم حيث يسهل رؤية اللون

- The starch is added near the end point.
- These titration are usually performed in neutral or mildly alkaline (pH=8) to weakly acid solution.
- If the pH is too alkaline ,I_2 will disproportionate to hypoiodate and iodide.

$$I_2 + 2OH^- = IO^- + I^- + H_2O$$

يستخدم عادة النشاء المنحل soluble Starch أي الذي يحتوي على كمية كبيرة من جزيئات الأميلوز الخطية من النمط بيتا الذي يقوم عمليا ببناء مركب حلقي مع ذرة اليود ، ويحضر هذا النشاء عادة من البطاطا أو الرز ، أما أنواع النشاء الأخرى الغنية بالأميلوز ألفا فلا تستخدم لأن تفاعلها غير عكسي وأما جزيء الأميلوبيكتين المتشعب فهو أصلاً غير منحل .

ولكي نضمن ثبات المحلول نضيف له يود الزئبق.

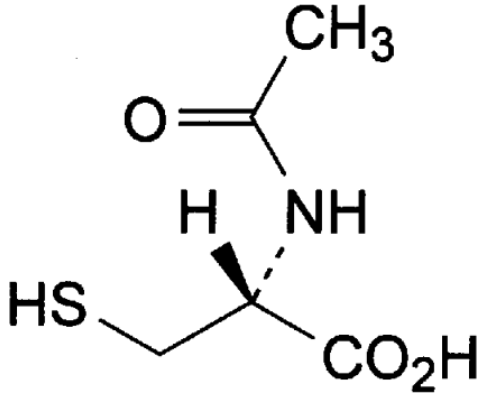
Iodimetry

There are three reasons for keeping the solution from becoming strongly acidic.

1. The starch used for the end point detection tends to hydrolyze or decompose in strong acid and so the end point may be affected.
2. The reducing power of several reducing agents is increased in neutral solution.
3. The third reason for avoiding acid solution is that the I^- produced in the reaction tends to be oxidized by dissolved Oxygen in acid solution:

$$4I^- + O_2 + 4H^+ \longrightarrow 2I_2 + 2H_2O$$

Assay of Acetylcysteine مثال : معايرة الأستيل سيستئين



C5H9NO3S **163.2** ***616-91-1***

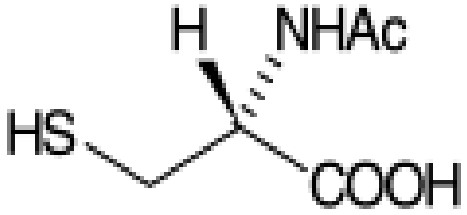
Action and use

Antidote for paracetamol poisoning; mucolytic.

Preparation

Acetylcysteine Injection

ACETYLCYSTEINE

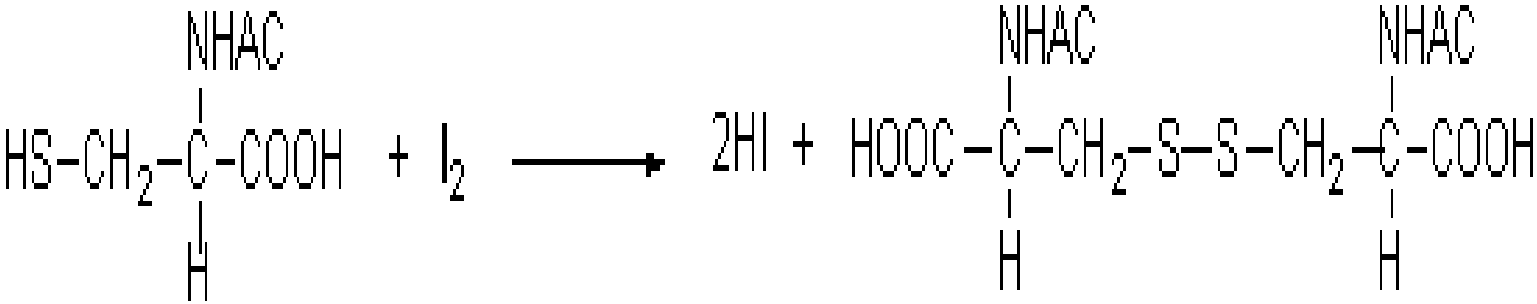


163.2 C5H9NO3S

Action and use Antidote for paracetamol poisoning; mucolytic.

Assay : Dissolve 0.3 g in 60 ml acetic acid 60% . And titrate with 0.05 M Iodine solution until yellow color.

1 ml of o.o5 M iodine solution is equivalent to 16.32 mg of $C_5H_9NO_3S$.



Iodometry ($S_2O_3^{--}$)

- In Iodometry ,the analyte is an oxidizing agent that reacts with I^- to form I_2.The I_2 is titrated with thiosulfate, using disappearance of starch-iodine color for the end point.
- $I_2 + 2S_2O_3^{-2} \longrightarrow 2I^- + S_4O_6^{--}$

Common titrants

Reducing titrants

- $S_2O_3^{2-}$ is not a primary standard material.
- It must be standardized using KIO_3.

$$IO_3^- + 5\,I^- + 6\,H^+ = 3\,I_3^- + 2\,H_2O$$

- KI is added to form I_3^-, which is water soluble.
- Although $S_2O_3^{2-}$ solutions are resistant to air oxidation, the tend to decompose:

$$S_2O_3^{2-} + H^+ \rightleftharpoons HSO_3^- + S_{(s)}$$

Common titrants

Reducing titrants

Iodide - indirect method

$2I^- = I_2 + 2e^-$

always

Can't be used directly due to it's intense color and reaction with air. $I^- + \text{light} \longrightarrow I_2$

Its more common to add excess iodide and use starch as an indicator.

Any iodine that is produced can be determined by titration with $Na_2S_2O_3$.

Common titrants

Iodide - indirect method

What happens is that

$$2I^- + Ox \longrightarrow I_2 + Red$$

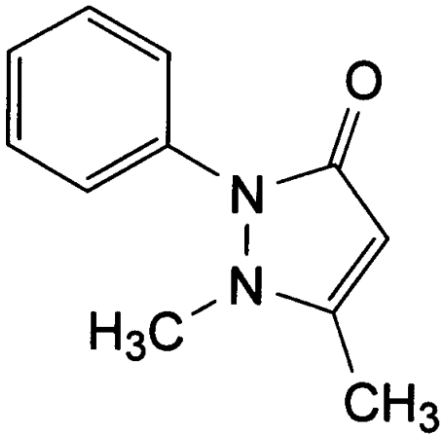
D

$$I_2 + 2\,S_2O_3^{2-} \longrightarrow 2I^- + S_4O_6^{2-}$$

It looks like it would just be easier to reduce our analyte with $S_2O_3^{2-}$ directly.

$Na_2S_2O_3 \equiv I_2 \equiv OX\ (D)$

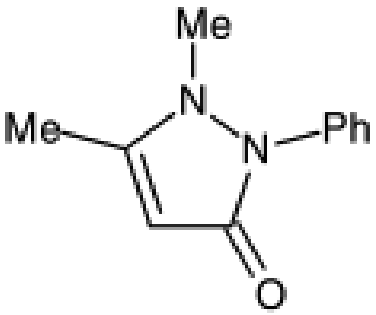
معايرة الفينازون :



تتم المعايرة بالرجوع حيث يعاير اليود الزائد بتحت كبريتيت الصوديوم

Iodometry (back titration)

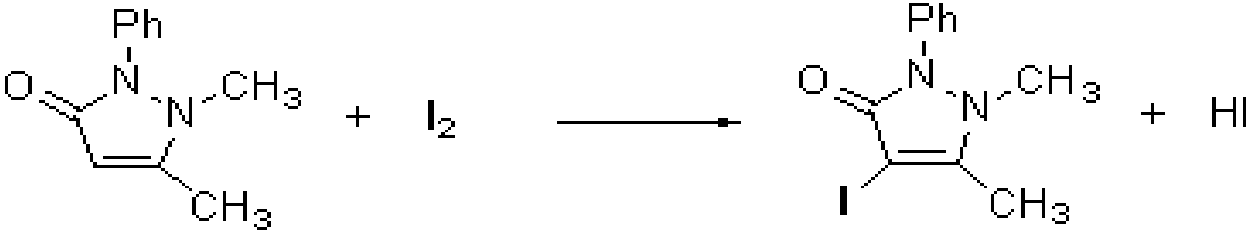
Phenazone = Antipyrine = Analgesic

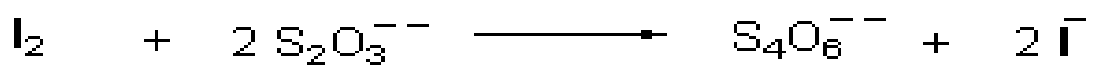


188.2 $C_{11}H_{12}N_2O$

Assay : Dissolve 0.150 g in 50 ml of water R. Add 2 g of sodium bicarbonate R, shake until the substance dissolves, and add 25.0 ml of 0.05 M iodine .Allow to stand protected from light for 30 min. Titrate with 0.1 M sodium thiosulphate , using 1 ml of starch solution R, added towards the end of the titration ,as indicator .Carry out a blank titration.

1 ml of 0.05 M Iodine is equivalent to 9.41 mg of $C_{11}H_{12}N_2O$.





معايرة الغلوكوز :

حيث تتم المعايرة بإضافة كمية فائضة من اليود بوجود هيدروكسيد الصوديوم ، حيث يقوم هذا الأخير بالتفاعل مع اليود محرراً كمية مكافئة من هيبوايوديد الصوديوم التي تتفاعل بدورها مع الغلوكوز والقسم الفائض منها نعامله مع حمض الكبريت الذي يحرر كمية مكافئة من اليود الذي يعاير بتحت الكبريتيت بوجود النشاء

Determination of Glucose in Liquid forms:

Assay : Pipette 10 ml of glucose solution in to conical flask. Dilute to 50 ml with water and add 40 ml of 0.1 M Iodine. Add 5 ml NaOH 0.1 N, Then stopper the flask, stand for 10 minutes. Acidify with 5 ml dil.H_2SO_4,Titrate with 0.1 M $Na_2S_2O_3$ using starch indicator .A blank experimental is carried out.

$$I_2 + 2\ NaOH \longrightarrow NaOI + NaI + H_2O$$

$$C_5H_{11}O_5.CHO + NaOI \longrightarrow C_5H_{11}O_5.COOH + NaI$$

$$2NaOI + H_2SO_4 \longrightarrow Na_2SO_4 + I_2 + H_2O$$

$$I_2 + 2\ Na_2S_2O_3 \longrightarrow 2\ NaI + Na_2S_4O_6$$

$$C_5H_{11}O_5.CHO = NaOI = I_2$$

Potassium Iodate (KIO_3)

- In acetic media the Iodate ion will oxidizer the Iodide to Iodine.

$$IO_3^- + 5I^- + 6H^+ \longrightarrow 3I_2 + 3H_2O$$

تستخدم لمعايرة صبغة اليود (اليود + اليودور)

Another example

Many REDOX reagents have been reported. Some get very specific. One good example is the Karl Fisher method for water.

$$2H_2O + SO_2 + I_2 \longrightarrow H_2SO_4 + 2HI$$

Karl Fisher reagent

A mixture of iodine, sulfur dioxide, pyridine and methanol.

Pyridine is necessary to shift the reaction to the right

$$C_5H_5N \cdot I_2 + C_5H_5NSO_2 + C_5H_5N \cdot HI + H_2O$$

$$2\ C_5H_5N \cdot HI + C_5H_5 \cdot SO_3$$

Water Karl-Fisher titration

$$2H_2O + SO_2.(C_5H_5N)_2 + I_2 + 2C_5H_5N \longrightarrow (C_5H_5N)_2.H_2SO_4 + 2C_5H_5N.HI$$

1 mole I_2 = 2 mole H_2O

Ammonium Cerium (IV) Sulphate

Titration

Ammonium Cerium(v) Sulphate Ceric ammonium sulphate; $2(NH_4)_2SO_4,Ce(SO_4)_2,2H_2O = 632.6$

$$Ce^{+4} + e^- \longrightarrow Ce^{+3} \quad n=1$$

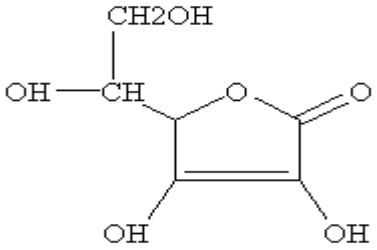
- E_0 =1.70 v (in $HClO_4$)
- E_0 =1.61 v (in HNO_3)
- E_0 =1.44 v (in H_2SO_4)
- E_0 =1.28 v (in HCl)

Ammonium Cerium (IV) Sulphate

Titration

- Cerium (IV) can be used for most titration in which permanganate is used and it possesses a number of advantages :
- It is very strong oxidizing agent (acidic M)
- The titration carried out in the presence of HCl and even in the presence of iron.
- The solution can be heated .
- Some cerium salt is a primary standard.

Pharmaceutical Application



- Ascorbic Acid Tablets (500 mg)

Assay : Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.15 g of Ascorbic acid as completely as possible in a mixture of 30 ml of water and 20 ml of 1 M sulphuric acid and titrate with 0.1 M ammonium cerium (IV) Sulphate VS using ferroin solution as indicator.

1- Calculate the weight of the sample. (incase 20tab=15 g)

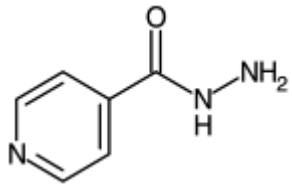
2- Calculate the miliequivalence using the Equation.

3- Assume we required to the end of the titration 17 ml ,what is the % of Ascorbic acid, and What is the Practical tablet contain .(F=1)

Br_2 or BrO_3- titration

- Brome solution is unstable therefore it produce during the titration using $KBrO_3$.
- $BrO_3^- + 5Br^- + 6H^+ \longrightarrow 3Br_2 + 3H_2O$ $E^0=1.44V$
- Back and replacement titration.
- The excess of Brome react with KI to give I_2
- $BrO_3^- + 6I^- + 6H^+ \longrightarrow 3I_2 + 3H_2O + Br^-$
- The Liberated Iodine will titrate with $Na_2S_2O_3$

Isoniazid Tablets 100 mg



C6H7N3O 137.1

Assay : Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 0.4 g of Isoniazid as completely as possible in water , dilute with water to 250 ml using volumetric flask. Transfer 25 ml of the resulting solution to stoppert conical flask, add 25 ml of 0.05 M Brome solution (Mixture of KBrO3 and KBr) and 5 ml of concentrated hydrochloric acid. Mix and let stand for 15 min. add 1 gram of potassium Iodide and titrate with 0.1 $Na_2S_2O_3$ using 1 ml of starch solution. Each ml of 0.05M Brome solution is equivalent to 0.003429 g of $C_6H_7N_3O$.

1. What is the weight of sample taken?(average weight =300mg)
2. write the titration equation.
3. Assume the consume volume of **0.1 $Na_2S_2O_3$ =13.5 and F=1 What is the % of Isoniazid in tablet and what is the Tablet contain ?**

1- 400 x 300 /100 = 1200 mg

Isoniazid

Br_2

Oxidation after 15 min.

Br_2-excess

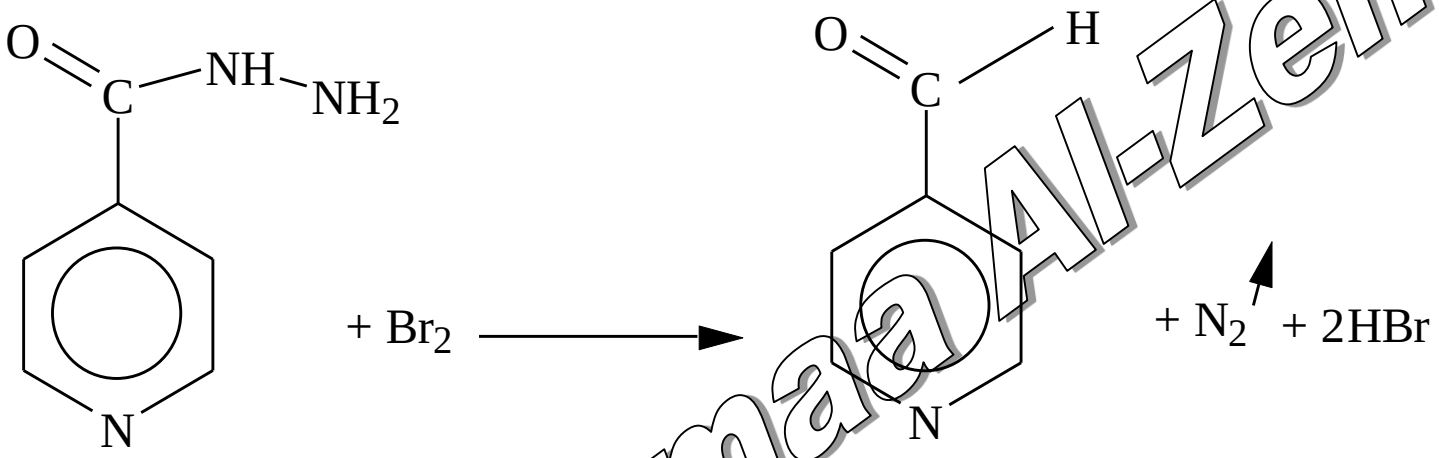
KI

I_2

$Na_2S_2O_3$

Back and replacement titration in the same time

$$(KBr + KBrO_3) + HCl \longrightarrow 3Br_2 + 3H_2O + KCl$$



$$3\ Br_2 + 6\ KI \xrightarrow{H^+} 3I_2 + 6KBr$$

$$2Na_2S_2O_3 + I_2 \longrightarrow 2NaI + Na_2S_2O_6$$

$$Na_2S_2O_3 \equiv I_2 \equiv Br_2$$

$$C\% = \frac{(25-13.5) \times 1 \times 0.003429 \times 100}{0.4} \times 10 = 97.6\%$$

Prof. J. Al-Zehouri

Q&A