Pharmaceutical Analytical Chemistry I

الأستاذ الدكتور جمعه الزهوري (دكتوراه صيدلة-ألمانيا 1991)

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Volumetric Precipitate titrations of Drugs (Argentimetry)

Precipitate Formation Titrations

As with other types of reactions, the formation of a precipitate can be used as the basis of a titration.

analyte + titrant ⟶ precipitate ↓

Drug cont.Halides — $AgNO_3$&NH_4SCN

The approach assumes that under the experimental conditions used, the product is virtually insoluble.

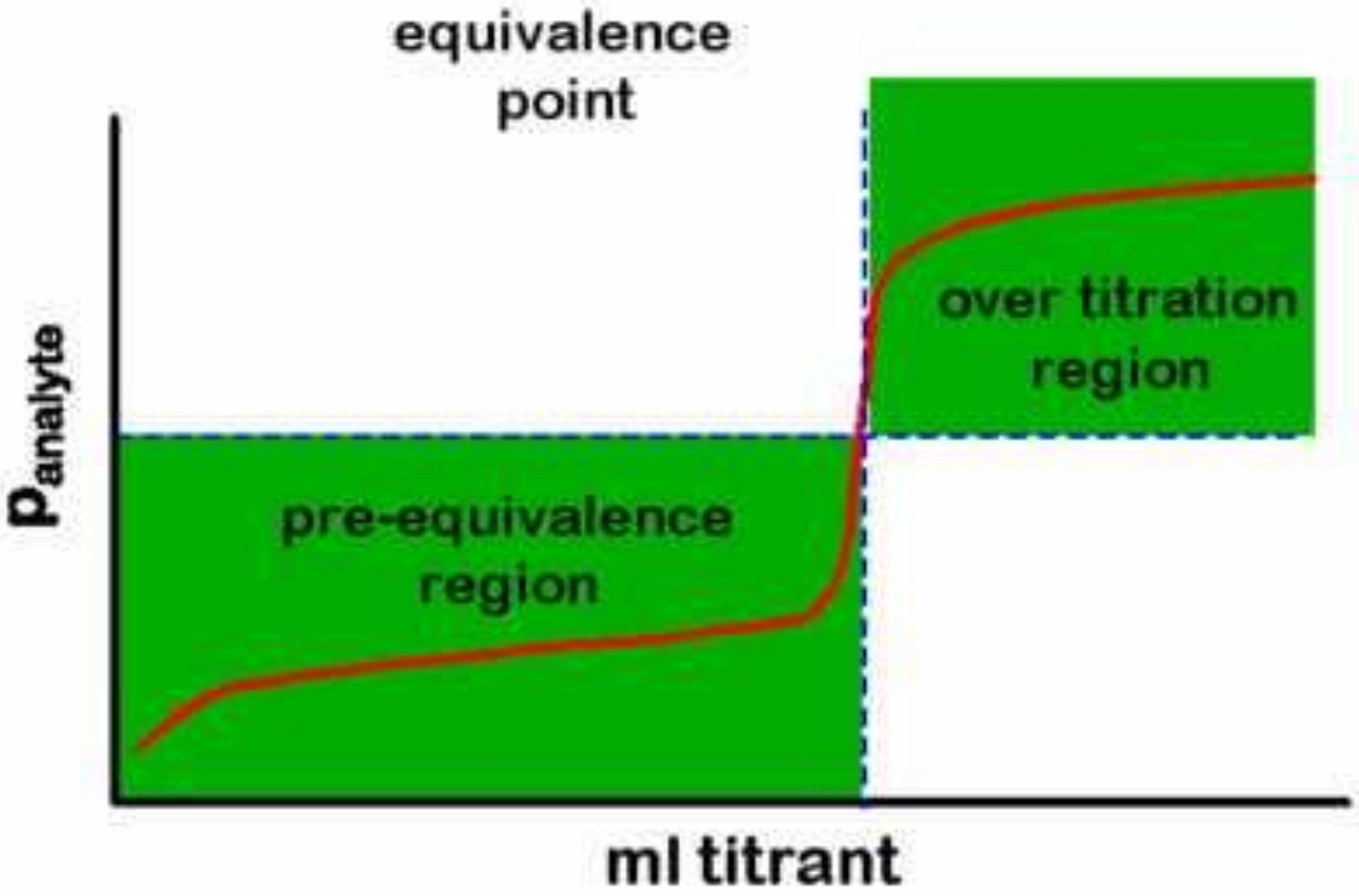
Preequivalence points

$pCl = -\log [Cl^-]$

ml titrant	total	$[Cl^-]$	pCl	$[Ag^+]$	pAg
0	50	0.1000	1.00	N/A	N/A
5	55	0.0818	1.09	2.20×10^{-9}	8.66
10	60	0.0667	1.18	2.69×10^{-9}	8.57
15	65	0.0539	1.27	3.34x10-9	8.48
20	70	0.0429	1.37	4.20x10-9	8.38
25	75	0.0333	1.48	5.41x10-9	8.27
30	80	0.0250	1.60	7.20x10-9	8.14
35	85	0.0176	1.75	1.02x10-8	7.99
40	90	0.0111	1.95	1.62x10-8	7.79
45	95	0.0053	2.27	3.40x10-8	7.47

Note: in all cases $[Cl^-] >> [Ag^+]$

Precipitate formation titration curves



Other methods for endpoint detection

Solubility (الأنحلالية،الذوبانية) هي أعلى كمية من المادة يمكن أن تذوب في حجم محدد من المذيب

Solubility Product (Ksp)جداء الأنحلال هو حاصل ضرب التركيز المولي لأيونات الراسب الذائبة بالمحلول

We'll review three approaches for endpoint detection of the $Ag^+ + Cl^-$ titration.

Mohr method	- competitive anion	التنافس الأيوني
Volhard method	- complex formation	تشكيل معقد
Fajans method	- absorption indicator	ادمصاص المشعر

Similar approaches can be applied to other precipitate formation titrations.

I - Mohr method for chloride

Solubility (الأنحلالية،الذوبانية) هي أعلى كمية من المادة يمكن أن تذوب في حجم محدد من المذيب
Solubility Product (Ksp) جداء الأنحلال هو حاصل ضرب التركيز المولي لأيونات الراسب الذائبة بالمحلول

This approach relies on K_{SP} differences for two insoluble silver salts.

$$K_{sp} = [Ag^+]\,[Cl^-] = 1.0 \times 10^{-10}$$

$$Ag^+ + Cl^- \longrightarrow AgCl \quad \text{(titration reaction)}$$

$$2\,Ag^+ + CrO_4^{2-} \longrightarrow Ag_2CrO_4 \quad \text{(at endpoint)}$$

$$K_{sp} = [Ag^+]^2\,[CrO_4^{-2}] = 1.9 \times 10^{-12}$$

AgCl is much less soluble than Ag_2CrO_4 so it will precipitate first.

Ag_2CrO_4 is brick-red in color so a color change is observed at the endpoint

I - Mohr method for chloride

pH

Must not conduct in acidic solutions

A pH of about 8 is best.

Blank

You should run a blank to determine how much you must over-titrate.

This is need for you to determine the amount of Ag_2CrO_4 that must be produced for you to be able to see it.

I- Mohr Method

- In acid media convert to dichromate:

$$2CrO_4^{--} + 2H^+ \rightleftharpoons Cr_2O_7^{--} + H_2O$$

Dichromate is more soluble

- In strong base media the silver will precipitate in form of hydroxide :

$$2Ag^+ + 2OH^- \rightleftharpoons 2\,AgOH \rightleftharpoons Ag_2O + H_2O$$

- The add of BORAX or Sodium bicarbonate well hold the pH at 8
- We can not determine the Iodide with this method because the precipitate of silver chromate will adsorb at the surface of silver iodide (adsorption complex) so the end point will be not clear.

II- Volhard method

This is an indirect method for chloride determination based on competitive complex formation.

Steps

Excess Ag^+ is added to the sample

AgCl is removed by filtration

Excess Ag^+ is titrated with SCN^-

Fe^{3+} acts as an indicator - it forms a complex with SCN^- after Ag^+ has all been consumed.

II- Volhard method

$$Ag^+ + Cl^- \rightarrow AgCl_{(s)} + \text{Excess } Ag^+$$

+

SCN^-

Fe^{3+} —endpoint→ $Fe(SCN)^{2+}$ (red)

Fe^{3+} + SCN^- ↓

$AgSCN_{(s)}$

The endpoint is not very sharp but gives good results.

II- Volhard method

- Titration reaction :

$SCN^- + Ag^+ \rightleftharpoons AgSCN$

- Indicator reaction :

$SCN^- + Fe^{+3} \rightleftharpoons Fe(SCN)^{+2}$ (red complex)

- This titration must be in acidic media to prevent the hydration of Fe^{+3} and formation of $Fe(OH)_3$

II- Volhard method

The Volhard method was first described by Jacob Volhard, a German chemist, in 1874.

Volhard method for chloride:

$$\underset{\textbf{excess}}{Ag^+} + Cl^- \rightleftharpoons \underset{\textbf{white}}{AgCl(s)}$$

$$SCN^- + Ag^+ \rightleftharpoons \underset{\textbf{white}}{AgSCN(s)}$$

$$Fe^{3+} + SCN^- \rightleftharpoons \underset{\textbf{red}}{Fe(SCN)^{2+}}$$

The Volhard procedure requires that the analyte solution be distinctly acidic.

III-Fajan ́s Method

- An Adsorption indicator method.
- **Adsorption** : is a process in which a substance (gas, liquid, or solid) is held on the surface of a solid. In contrast, **absorption** involves retention of a substance within the **pores** of a solid

III- Fajans method

This is an adsorption indicator method where the endpoint reaction occurs on the surface of the AgCl precipitate.

It relies on the change in the primary adsorbent ion which occurs when we go past the equivalence point.

$$Ag^{+} + Cl^{-} \longrightarrow AgCl$$

$$Ag^{+} + AgCl + Indic \longrightarrow AgCl{:}Ag^{+}\ Indic$$

Indicator - fluorescein

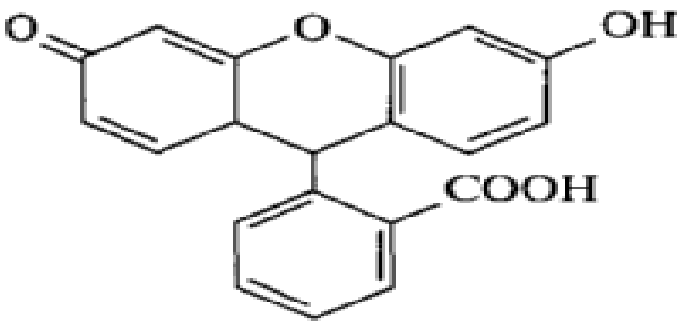
Fajan ُs Method

- **Adsorption Indicators**

  is an organic compound that tends to be adsorbed onto the surface of the solid in a precipitation titration , Ideally, the adsorption (or desorption) occurs near the equivalence point and results not only in a color change but also in a transfer of color from the solution to the solid (or the reverse)

Fajan ُs Method

- **Fluorescein** :is a typical adsorption indicator useful for the titration of chloride ion with silver nitrate .In aqueous solution , fluorescein partially dissociates into hydronium ions and negatively charged fluoresceinate ions that are yellow-green.
- The fluoresceinate ion forms an intensely red silver salt. Whenever this dye is used as an indicator, however ,its concentration is never large enough to precipitate as silver fluoreceinate.

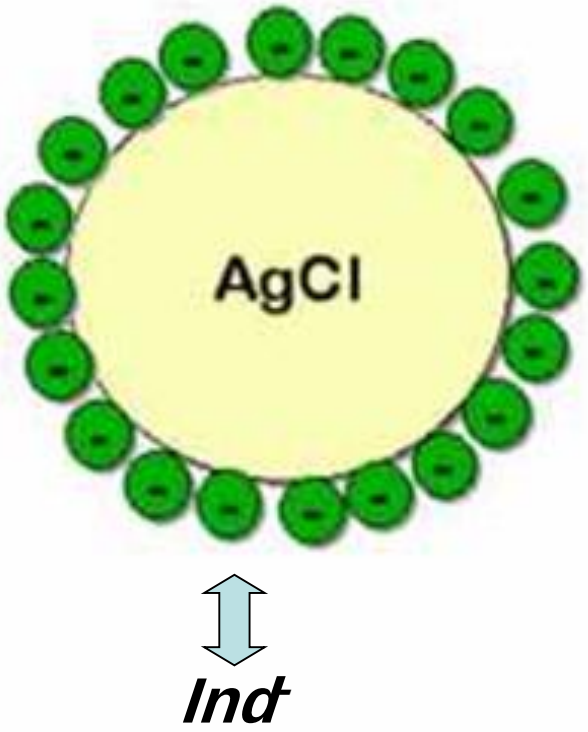


fluorescein

•In the early stage of the titration of chloride ion with silver nitrate ,the colloidal silver chloride particles are negatively charged because of adsorption of excess chloride ions .[A colloid is a solid made up of particles having diameters that are less than 10^{-4} cm)

Fajans method

Prior to reaching the equivalence point.



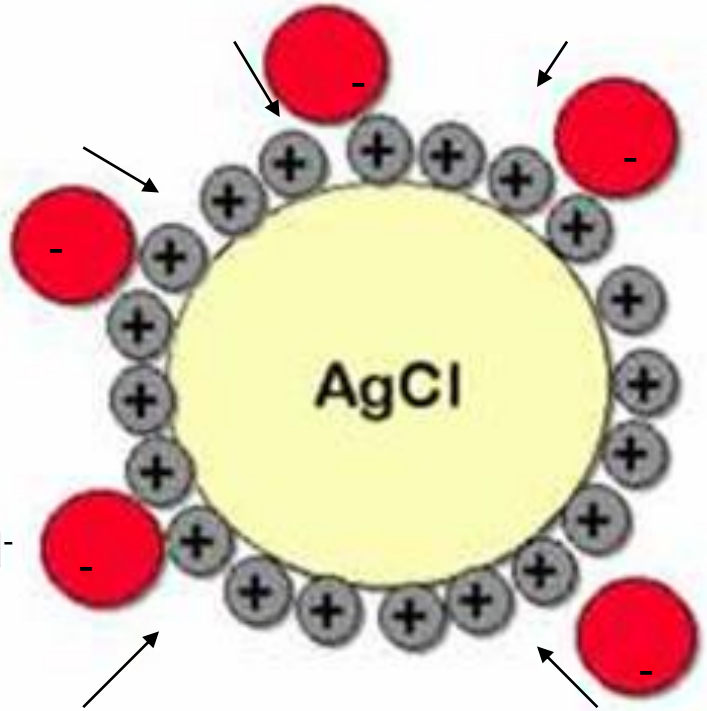
Until we reach the equivalence point, chloride is in excess.

It is our primary adsorbed ion.

The outer surface is negative which acts to repel the indicator.

Fajans method

After passing the equivalence point.



After the equivalence point, silver ion is in excess.

It becomes our primary adsorbed ion.

Our indicator can now be attracted to the surface.

Adsorption indicators

Factors affecting the adsorption endpoint.

- Intensity of color is determined by the number of indicator molecules adsorption
- Dependent on indicator concentration and ppt surface area.
- The indicator ion must not be able to displace the primary adsorbed ion.
- It must be adsorbed by the counter ion present at the endpoint.

The order of the ability of anions to replace the adsorpant anions on the silver halide surface

1. I^-, CN^-	5. Cl^-, dicloroflurescein anion
2. SCN^-	6. fluorescein anion
3. Br^-	7. NO_3^-
4. eosin anion	8. ClO_4^-

نستخدم الأيوزين لمعايرة البروم وليس الكلور والفلوريسن لمعايرة الكلور وليس النترات

أيونات المشعر يجب أن لا تملك القدرة على ازاحة طبقة الأدمصاص الأولية

Adsorption indicators

Factors affecting the adsorption endpoint.

The pH must be high enough to prevent conversion of Indic to HIndic.

$$HIn \rightleftharpoons H^+ + In^-$$

High ionic strength may favor the ionization of the Ag^+ : Indic pair, altering the endpoint.

A large surface area may increase photodecomposition of AgCl.

You must work in diffuse lighting.

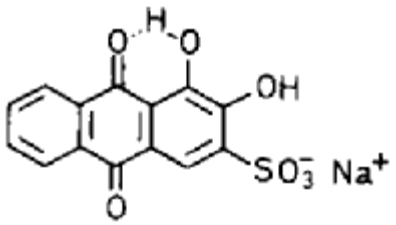
- **Colloidal precipitate is necessary**
- **Avoiding heating to prevent the Coagulation**

Other adsorption indicators

Yes, we can actually use the approach for other something other than chloride.

Another example

Alizarin red S



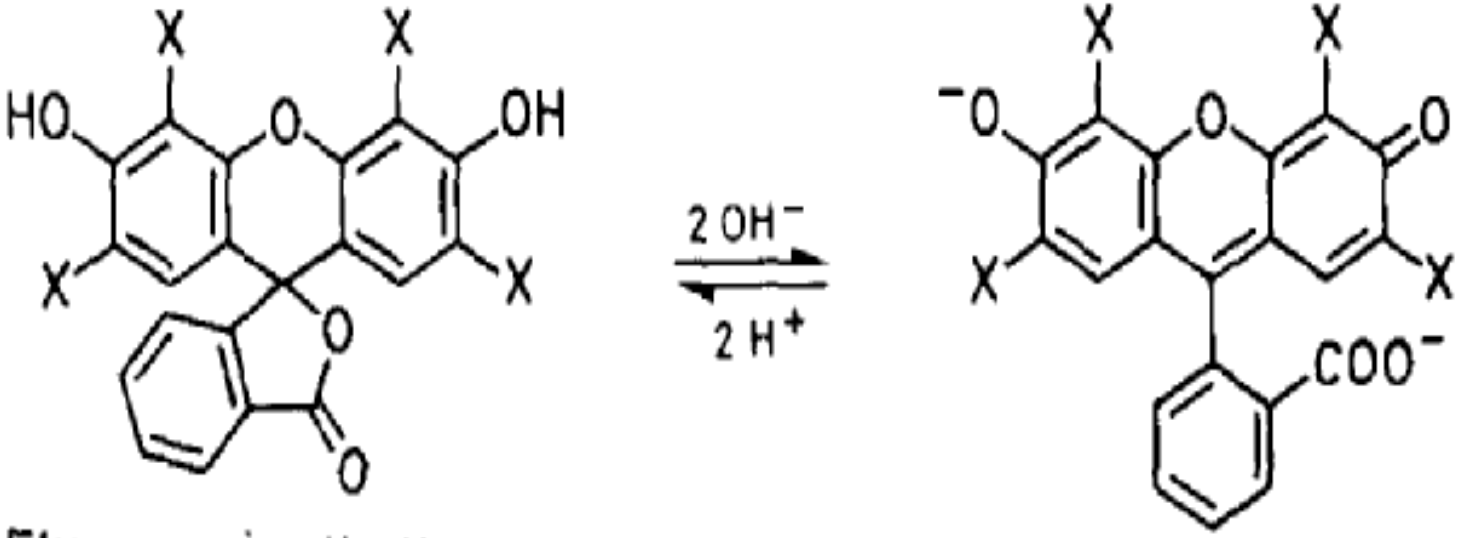
Alizarin - S

Indicator for the determination of sulfate by titration with barium

The approach gives results comparable to a gravimetric analysis but is typically more rapid.

Adsorption Indicators in Argentimetry

Indicator	Titration	pH (range)
Fluorescein	Cl^- with Ag^+	7-8
Dichlorofluoure scein	Cl^- with Ag^+	4
Bromocresol green	SCN^- with Ag^+	4-5
Eosin	SCN^-,I^-,Br^- with Ag^+	2



Fluorescein X = H

Eosin X = Br

Argentimetric titration is used in pharmacopoeial assays of :

Sodium Chloride Tablets

Potassium Chloride Tablets

Thiamine hydrochloride (Vit.B)

Mustine Hydrochloride)

Sodium Chloride 58.44 NaCl

Action and use Used in treatment of electrolyte deficiency.

Preparations

Oral Rehydration Salts

Potassium Chloride and Sodium Chloride Intravenous Infusion

Potassium Chloride, Sodium Chloride and Glucose Intravenous Infusion

Sodium Chloride Eye Drops

Sodium Chloride Eye Lotion

Sodium Chloride Intravenous Infusion

Sodium Chloride and Glucose Intravenous Infusion

Sodium Chloride Irrigation Solution

Compound Sodium Chloride Mouthwash

Sodium Chloride Solution

Sodium Chloride Tablets

Sodium Chloride

ASSAY

Dissolve 1.000 g in *water* and dilute to 100 ml with the same solvent. To 10.0 ml of the solution add 50 ml of *water*, 5 ml of *dilute nitric acid*, 25.0 ml of *0.1*M *silver nitrate*. Shake. Titrate with *0.1*M *ammonium thiocyanate*, using 2 ml of *ferric ammonium sulphate solution* as indicator and shaking vigorously towards the end-point.

1 ml of *0.1*M *silver nitrate* is equivalent to 5.844 mg of NaCl.

Sodium Chloride Eye Drops

Content of sodium chloride, NaCl

90.0 to 110.0% of the stated amount.

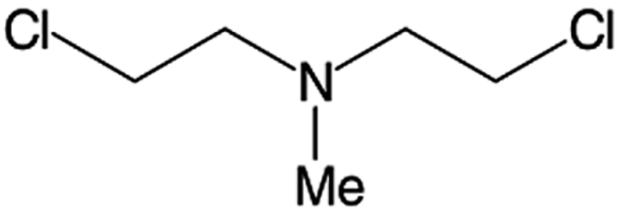
ASSAY

Titrate a volume containing 0.1 g of Sodium Chloride with 0.1M *silver nitrate VS* using *potassium chromate solution* as indicator. Each ml of 0.1M *silver nitrate VS* is equivalent to 5.844 mg of NaCl.

Mohr

Chlormethine Hydrochloride (Mustine Hydrochloride)

NOTE: The name Mustine Hydrochloride was formerly used in the United Kingdom.



,HCl

C5H11Cl2N,HCl 192.5 *55-86-7*

Action and use

ذو تأثير سمي على الخلايا Cytotoxic.

Preparation

Chlormethine Injection

ASSAY

To 0.2 g add 15 ml of 1M *ethanolic potassium hydroxide* and 15 ml of *water* and boil under a reflux condenser for 2 hours. Evaporate the solution to half its volume on a water bath, dilute to 150 ml with *water* , add 3 ml of *nitric acid* and 50 ml of 0.1M *silver nitrate VS*, shake vigorously and filter. Wash the residue with *water* and titrate the excess of silver nitrate in the combined filtrate and washings with 0.1M *ammonium thiocyanate VS* using 1 ml of *ammonium iron(III) sulphate solution R2* as indicator. Each ml of 0.1M *silver nitrate VS* is equivalent to 6.418 mg of C5H11Cl2N, HCl.

Analytical Applied

- A mixture containing only KCl and NaBr is analyzed by the Mohr method. A 0.3172 g sample is dissolved in 50 ml of water and titrated to the Ag_2CrO_4 end point, requiring 36.85 ml of 0.1120 M $AgNO_3$. A blank titration requires 0.71 ml of titrant to reach the same end point. Report the %w/w KCl and NaBr in the sample.

Prof. J. Al-Zehouri

Q&A