De complexometrische titratiemethode bij het onderzoek van geneesmiddelen
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SUMMARY

Complexometry is a titration method for quantitative determination of metals with the aid of so-called complexones, certain substances which form chelate-complexes with the metal ions.

This method has been developed by Schwarzenbach and co-workers during the last ten years. It is in rapid progress today. Many applications for practical purposes have already been published.

In this dissertation the possibility of using the complexometric titration method in pharmaceutical analysis has been investigated. The use as a standard pharmacopoeial method for determining calcium, magnesium, strontium, barium, lead, zinc, mercury, aluminium and bismuth in pharmaceutical compounds, to be found in the International Pharmacopoeia of the World Health Organisation and in the Netherlands Pharmacopoeia has especially been pointed out. Several drugs, appearing in the United States Pharmacopeia (XIVth revision), the British Pharmacopoeia (1953), the National Formulary (Washington, IXth edition), the Codex Medicamentorum Nederlandicus and the British Pharmaceutical Codex (1954) have also been investigated.

This has been done for the purpose of uniforming methods of quantitative analysis in the pharmacopoeias, and of giving reliable methods, — which are as a rule much quicker than the existing official assays — to the practising pharmacist as well as to the analytical chemist in pharmaceutical control-laboratories.

In Chapter 2 the properties of chelate-complexes have been discussed in connection with their significance for the analytical chemistry in general and for the pharmaceutical analysis in particular. In Chapter 3 and 4 items and investigations are given about complexones, titrants, indicators and remaining reagents, their preparation, their tenability, their quantitative determination. The methodics, the apparatus etc. have also been described here.

The only complexone-titrant used in this dissertation is a 0,1 n solution of the disodiumsalt of ethylenediamine-N-N'-tetra-acetic acid. (complexone III, disodiumversenate).

Chapters 5 to 8 deal with the determination of the metals in pharmaceuticals (chapter 5: earth-alkalies; 6: zinc and mercury; 7: lead; 8: aluminium and bismuth).

The complexometric behaviour of the various metals has been
reviewed in connection with the other metals in the respective groups of the periodic system.

In each chapter the methods of analysis now in use in the pharmacopoeias have been discussed. As a result of this discussion a reference method has been chosen. The results obtained with the complexometric methods have been compared with those, obtained with the reference method. In several cases a reference method has been pointed out first. Thus investigations have been made of various non-complexometric analyses, such as the gravimetric and titrimetric analysis of calcium as calciumoxalate and the determination of barium as bariumsulfate.

In chapter 5 (earth-alkalimetals) special attention has been paid to the quantitative determination of mixtures of calcium and magnesium in several ratios.

A complexometric titration with 0,1 n complexone III solution has been pointed out of calcium and magnesium, in a ratio up to 1 : 12, the absolute quantity of magnesium being about 250 mg. It has been shown that the ratio Ca/Mg as well as the absolute concentrations of these metals are of great importance. The influence of anions of hydroxyacids, (lactic acid, citric acid, tartaric acid) has also been investigated, because these anions are frequently appearing in pharmaceuticals. The results are tabled in series of at least 4, in general 6 complexometric determinations of each method and of each drug.

The mean and the standarddeviation ($s_w$) has been given.

$$s_w = A(n)w,$$

where: $s_w$ = standarddeviation.

$w$ = difference between highest and lowest result.

$A$ = factor; for $n = 4$ is $A = 0.49$

for $n = 5$ is $A = 0.43$

for $n = 6$ is $A = 0.40$.

On condition that the determination is performed in the manner described in this dissertation, the complexometric method can be recommended as a quantitative method for pharmacopoeial purposes ("assay") for a lot of drugs.

1. Calcium: Recommended for Calcii Carbonas, Calcii Hydroxydum, Calcii Chloridum, Calcii Bromidum, Calcii Phosphas (CaHPO$_4$), Calcii Phosphas tribasicus (Ca$_3$(PO$_4$)$_2$), Calcii Lactophosphas, Calcii

Compared with the existing quantitative methods the complexometric method gives a great improvement, because it is quicker and yet easy to reproduce. The results of the "classical" methods and of the complexometric methods agree very well on the whole.

In a few cases a removal of the anion is desirable or necessary.

2. Magnesium: Recommended for Magnesii Oxydum, Magnesii Carbonas, Magnesii Chloridum, Magnesii Sulfas, Magnesii Thiosulfas, Magnesii Peroxydum, Magnesii Citras, Magnesii Stearas. With Magnesii Peroxydum the complexometric titration can be performed following up the alcalimetric titration of the residue of ignition. (The alcalimetric titration is found in the Codex Medicamentorum Nederlandicus).

3. Strontium: The method is well reproducible, but the results obtained with pharmaceuticals are, in general, higher than those obtained with the gravimetric determination as strontiumsulfate. As strontium-compounds (pharmaceutical purity) frequently contain a little calcium, the high results may be due to the calcium content (discussion in 5.8.2). With this restriction the complexometric method may be applied to Strontii Chloridum, Strontii Carbonas and Strontii Sulfas.

4. Barium: The method may be applied to Barii Chloridum. It is unusable in the analysis of Barii Sulfas.

5. Zinc: The complexometric method can be recommended for Zinci Chloridum, Zinci Sulfas, Zinci Oxydum, Zinci Sulfophenylas, Zinci Acetas, Zinci Valerianas, Zinci Undecylenas, Zinci Stearas. The complexometric method is warmly recommended for all pharmaceutical zinc-compounds mentioned above, because it is a very accurate method and the standard deviation is very small. Especially for zincstearate (and other salts of higher fatty acids) the complex-

* Drugs thus marked have been inserted in the International Pharmacopoeia first edition, World Health Organization, Geneva, 1951—1954.
ometric method is much better than the one, described in the U.S.P. XIV (see 6.2.9).

6. Mercury: Inorganic mercury-compounds. The pharmacopoeial methods, now in use, are of a great variety, but they are not time consuming. In this respect there is no argument for using complexometric methods. Moreover the classical methods are more selective. The complexometric method was recommended by Hernandez c.s. (6.4.2) because it is more uniform than the older ones.

Complexometry can be applied to Hydrargyri Bichloridum*, Hydrargyri Oxydum*, Hydrargyri Aminochloridum* and (after destruction) to Hydrargyri Iodidum rubrum*.

Organic mercury-compounds. A destruction must be carried out before the complexometric titration can be applied. As in the existing methods after destruction the titration of mercury is carried out with rhodanide, here, too, a gain of time cannot be obtained by using complexometric methods.

The complexometric method cannot be recommended for Hydrargyri Salicilas and Hydrargyri Oxycyanidum. The destruction of Merbromine gives difficulties, and on the other hand the method of Denoël (6.4.2) is very simple, so this method is preferable.

The complexometric titration can be applied to Mercurisuccinimidum, Nitromersolum, Phenylhydrargyri Nitrats* and Mersalylum*.

7. Lead: The method can be recommended for Plumbi Oxydum, Plumbi Acetas, Solutio Plumbi Subacetatis, Plumbi Subcarbonas. The complexometric methods are quicker and easy to reproduce.

8. Aluminium: The development of complexometric methods for determination of aluminium is in rapid progress at present. The titration method according to the principle of Ter Haar and Bazen (8.2.3) has been investigated and applied.

This method requires some experience and the use of a pH-meter is highly desirable. The method is much quicker than the various gravimetric methods. On that account the complexometric method is recommended for Aluminii Chloridum, Aluminii Sulfas, Aluminii et Kalii sulfas, Solutio Aluminii Acetatis. It can be applied to Solutio Aluminii Acetatis cum Plumbi Sulfate (Solutio Burowi). It can not be recommended for Aluminii Hydroxydum colloideum and Aluminii Acetotartras.

Complexometric titrations of iron will be subject to separate investigations. Therefore the application of the titration of aluminium by backtitration of complexone III with Fe<sup>3+</sup>-solution, as recently
published by MILLER and WOOLHEAD (114), has not been investigated in this dissertation. According to SCHWARZENBACH (145) this method is not very accurate.

His unfavourable judgment on the method of TER HAAR and BAZEN may be due to the poor pH-setting. TER HAAR and BAZEN don’t use a pH-meter, but it should be done.

For the pharmaceuticals mentioned above, the method of TER HAAR and BAZEN is certainly to be preferred to the existing pharmacopoeial methods. It may be that one doesn’t yet want to introduce the complexometric titration of aluminium in the pharmacopoeia, because of the non-stabilised situation in this field. It has been pointed out in this dissertation, that in any case the gravimetric aluminium-determination according to the principle of WILLARD and TANG (succinate-method) is preferable to the precipitation of aluminium with ammonia.

9. Bismuth: The method of GRÖNKVIST is a very good one, but it is rather expensive. It has been stated that bismuth titrations with complexone III, using eriochromeblack T as indicator, must be carried out between pH = 8.8 and pH = 9.0. The method according to the principle of TER HAAR and BAZEN gives somewhat lower results than those obtained with other complexometric methods.

The advantage of the method TER HAAR-BAZEN is, that a destruction of organic material is nearly always unnecessary, while the other complexometric methods must in general be preceded by a destruction. Of the existing pharmacopoeial methods the gravimetric determination as Bi₂O₃ by evaporating with nitric acid of iodine containing bismuth-compounds, must in any case be replaced. This method gives too low results. Determination as bismuthphosphate is accurate, but time consuming, when compared with the complexometric methods. The complexometry can be recommended for Bismuthi Subcarbonas*, Bismuthi Subnitras*, Bismuthi Hydras, Bismuthi Lactas, Bismuthi et Natrii Tartras, Bismuthi Subsulicipias*, Bismuthi Subgallas, Bismuthi Oxyiodidogallas, Bismuthi Tribromphenylas and Bismuthi Tetrabrompyrocatechin.

The development in the field of complexometric bismuth-determinations promises many possibilities in the future. E.g.: SCHWARZENBACH (145) has just published that the indicator pyrocatecholviolet, introduced for bismuth titrations by MALAT et al. (99), gives very good results. Destruction or decomposition of the organic bismuthcompounds will remain necessary until stronger complex-forming agents will
have been found, which might take up the bismuth without preceding destruction of organic matter. The results obtained with the procedures described in this dissertation, are so favourable that direct use of complexometric methods of bismuth determination for pharmacopoeial purposes can be recommended. One need not wait until other methods have been developed. If a new developed method should be much better than the existing complexometric methods, it could be introduced in the pharmacopoeia by supplement.