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# Spectrophotometric determination of cobalt in multivitaminic preparations with dipyridylglyoxal mono(2-pyridyl)hydrazone

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## Summary

A brief review on the determination of cobalt in pharmaceutical preparations as well as the spectrophotometric determination of cobalt in Hidropolivit Mineral — a complex multivitamin preparation — with the use of dipyridylglyoxal mono(2-pyridyl)hydrazone are reported in this paper. A procedure in which preliminary ashing is eliminated is followed in the sample preparation. Preliminary experiments were carried out in order to check that the presence of various vitamins and hormones had no adverse effects on the recovery of cobalt. Comparison of the variance and mean values obtained for cobalt in Hidropolivit Mineral by the proposed method ($\bar{x} \pm$ S.D. = 0.029 ± 0.003 mg of cobalt per tablet) and the biacetyl mono(2-pyridyl)hydrazone method for cobalt ($\bar{x} \pm$ S.D. = 0.026 ± 0.002 mg of cobalt per tablet) using the variance ratio test and Student's $t$-test showed no significant differences between the two methods.

## Introduction

Though most therapeutic drugs are derived usually of organic compounds, a number of metallic elements which have considerable pharmacological interest are still widely used (Rousselet and Thuillier, 1979). Cobalt is used as a biocatalytic medication and it is also a component of vitamin $B_{12}$ (cyanocobalamin). Salts of cobalt(II) are commonly present in combination with other mineral salts and hormones in geriatric preparations as they are present in combination with other minerals and vitamins in multivitaminic preparations (Eldewy and Elshabouri, 1975; Eldewy et al., 1976).

The analysis of metallic elements in pharmaceutical preparations present a difficult problem due to the matrix. In addition, pharmaceutical tablets may contain extra ingredients such as coloured coating (Vandenbalck et al., 1979) in order to improve visual acceptability of the preparation as well as its rapid identification. Moreover, pharmacopeias often prescribe the determination of metal ions in drugs in which they are considered to be impurities (Becket and Stenlake, 1975), derived either from the raw materials or remained from the reagents employed in their synthesis, e.g. some hydrofining catalysts.

The determination of metal ion in pharmaceuti-

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cal preparations is a prerequisite for routine plant control analysis. In a previous paper (Asuero et al. 1987) we have examined dipyridylglyoxal mono (2-pyridyl)hydrazone (DMPH) as a valuable reagent for the spectrophotometric determination of cobalt, a method proposed for the determination of cobalt in synthetic mixtures of foreign ions. The method devised has been applied in this report to the determination of cobalt in Hidropolivit Mineral, a complex pharmaceutical multivitamin preparation. The DMPH method for cobalt has been compared with one previously published which involves the use of biacetyl mono(2-pyridyl)hydrazone (Asuero and Rodriguez, 1980) as a chromogenic reagent. Results obtained in both cases were in good agreement. However, previous to the application of the DMPH method to the determination of cobalt in Hidropolivit Mineral a brief review on the determination of cobalt in pharmaceutical preparations is given.

### *Brief review on the determination of cobalt in pharmaceutical preparations*

Complexometry has been used in the determination of traces of cobalt and other ions in admixtures with vitamins (Blagojevic et al., 1964), but in the case of cobalt failed to give good results. Polarography has been successfully employed in the determination of cobalt in admixture with vitamin $B_2$ and vitamin C in tablets and ampoules (Sterescu et al., 1959) and spectrography has been applied instead to the determination of cobalt (Farhan and Makhani, 1970) in vitamin $B_{12}$ preparations. Thiocyanate in the presence of ammonium fluoride (Guerello, 1970), 5-(2-hydroxy-1-naphthylazo)-pyrazole-4-carboxylic acid (Janik and Gancarcyk, 1974), 3-methyl-1-thiocarbamoyl pyrazolin-5-one (Gormak, 1974), 7-nitroso-8-hydroxyquinoline-5-sulphonic acid sodium salt (Eldewy et al., 1976), 3 dyes of the 1,3,4-thiadiazolylazophenol group (Domagalina and Zareba, 1977), picolinamidoxime 1-oxide (Zommer-Urbanska and Rzeszowska-Modzelewska, 1983) and picolin-2-aldoxime (Losada del Barrio et al., 1986), have been employed as chromogenic reagents for the spectrophotometric determination of cobalt in pharmaceutical preparations. However, in practically all of these methods of analysis it is necessary to destroy the organic matter as the primary step. This destruction of the organic matter made the methods cumbersome and time-consuming and were unsuited for routine work in industrial laboratories. Sample preparation may be reduced to a minimum by employing the technique of acid dissolution before atomic absorption spectrophotometric determination (Leaton, 1970; Smith, 1973; Rousselet and Thuillier, 1979; Ali, 1984; Eider, 1971). Cobalts has been determined in tablets containing cobalt sulphate, copper sulphate and iron sulphate (Leaton, 1970), and in vitamin $B_{12}$ after extraction of tablets with hot water (Berge et al., 1968). Chelation of cobalt by corrin-skeleton vitamin $B_{12}$ does not interfere in conversion of the metal ion to the atomic state in the burner flame, according to Berge et al. (1968). Other authors prefer wet mineralization of vitamin $B_{12}$ (Rousselet and Thuillier, 1979). A preliminary ion-exchange separation is carried out by Korkisch and Hübner (1976) in the determination of cobalt and other metal ions in multivitamin preparations, before application of atomic absorption spectrophotometric determination. Flameless atomic absorption spectrophotometry after dissolution of powdered tablets in 1% dilute hydrochloric acid has been applied instead by Kosonen et al. (1978) in the analysis of cobalt in multivitamin preparations.

Several papers have been published dealing with the detection of impurities, including cobalt, in pharmaceuticals and pharmaceutical preparations. Thus, several metal ions including cobalt were detected in pharmaceutical preparations (sodium phenobarbital, sulphacetamide sodium, acetarsol, glutamic acid and *p*-aminobenzoic acid) by the use of thin-layer chromatography; dithiozonate of cobalt was analysed on chromatographic plates covered with silica Gel G (Pawlaczyk and Sierzant, 1974). Cobalt in vegetable drugs has also been detected by thin-layer chromatography (Gill and Luczkiewicz, 1977). The ring oven technique has been employed (Pawlaczyk and Nowacka, 1978) for determining trace impurities of metal ions in pharmaceuticals. Thin-layer chromatographic detection limits of cobalt ions in different absorption coating has been reported (Thielemann, 1980). Diphenyldithiocarbaminate has been used as a coprecipitant in the routine determination of 12 heavy metals including cobalt in pharmaceuticals (Linder et al., 1978) by X-ray fluorescence spectroscopy after decomposition of the samples with sulphuric acid and hydrogen peroxide in a temperature-programmed digestion apparatus. Levels of cobalt have been determined in *p*-aminosalicylic acid sodium salt, phenylbutazone and hydantoin by atomic absorption spectrophotometry (Pawlaczyk and Makowska, 1979) once the samples were mineralized.

It can be concluded after this brief summary that the spectrophotometric analysis of cobalt(II) in multicomponent pharmaceutical preparations has not been frequently reported. Sophisticated techniques are usually used in the determination of metal ions in real-life samples in well-equipped laboratories, but all these methods involve expensive instrumentation. Moreover, there is still great interest in the analytical methods employing good chromogenic reagents for estimation of metal ions. The dipyridylglyoxal mono(2-pyridyl)hydrazone (DMPH) spectrophotometric method offers the possibility of an accurate, specific and easy determination of cobalt in a complex matrix without previous separation as can be seen in the following.

## Materials and Methods

### *Apparatus*

The apparatus used was the same as previously indicated (Asuero et al., 1986).

### *Reagents*

Dipyridylglyoxal mono(2-pyridyl)hydrazone: prepare a 0.04% w/v solution in ethanol. The reagent is synthesized from dipyridylglyoxal and 2-hydrazinopyridine (Chiswell et al. 1964).

Standardised solution of cobalt: 3.9985 g/liter. A working solution of 50 μg/ml was prepared by appropriate dilution.

Disodium hydrogen citrate, $C_6H_6O_7Na_2 \cdot 11/2\ H_2O$ (BP, Carlo Erba), 10% m/v in distilled water.

Thiourea (Merck), 12.5% w/v solution in dimethylformamide (Merck). Prepare fresh as required.

70% Perchloric acid (Merck).

The following commercially available vitamins were used: vitamin A palmitate, 1,700,000 I.U./g (Carlo Erba); vitamin E acetate, 98% (Carlo Erba); vitamin $K_1$, phytomenadion (Merck); vitamin $B_6$, piridoxine monohydrochloride (Sigma); vitamin $B_1$, thiamine chlorohydrate (Carlo Erba), vitamin C, L-(+)-ascorbic acid 99% (Carlo Erba); vitamin $D_3$ (Merck); vitamin $B_2$, Riboflavin (Scharlau); folic acid (Merck); *p*-aminobenzoic acid (Carlo Erba) and Nicotinamide (Scharlau). The hormones estradiol (Merck) and testosterone (Merck) were also used.

All common reagents were of analytical reagent grade or a sufficient purity for the purpose intended. Glass-distilled water was used throughout for dilution purposes.

### *Determination of cobalt in Hidropolivit Mineral*

Weigh and pulverize 6 tablets of Hidropolivit Mineral (Menarini Laboratories, Badalona, Spain). Accurately weigh and transfer to a 50-ml beaker a quantity of powder equivalent to 3 tablets (5.8778 g of powder), add 25 ml of distilled water, 1.5 ml of 60% perchloric acid and dissolve by heating gently with magnetic stirring during 0.5 h. Allow the solution to cool and filter through a Whatman no. 42 filter into a 50-ml volumetric flask, and then dilute to volume with distilled water. By pipet, introduce aliquots of 2.5 ml of this solution into 25-ml calibrated flasks, add 5 ml of di-sodium hydrogen citrate at 10% in water and 1.25 ml of thiourea at 12.5% in dimethylformamide, adjust the pH to 4–7 by adding dilute sodium hydroxide solution (check in a separate sample the necessary amount of sodium hydroxide to get this), add 6 ml of dipyridylglyoxal mono(2-pyridyl)hydrazone at 0.04% in ethanol and mix the solutions thoroughly. Add 2.15 ml 70% perchloric acid and dilute to the mark with distilled water. Measure the absorbance at 510 nm in a glass cell of 10 mm path length against a reagent blank prepared following the procedure from "add 6 ml of dipyridylglyoxal mono(2-pyridyl)hydrazone at 0.04% in ethanol...". As the sample is colored, pipette another sample aliquot at the same time so that the background absorbance can be determined. Treat this second aliquot in the same manner as the test solution without the addition of dipyridylglyoxal mono(2-pyridyl)hydrazone (but adding 6 ml of ethanol instead). Measure the background absorbance against a solvent blank and subtract it from the absorbance of the test solution. Convert the absorbance reading into μg/ml of cobalt by referring to the calibration curve calculated as follows. Carry 0.12, 0.20, 0.25, 0.50, and 0.75-ml portions of a 50 μg/ml standard cobalt solution through the procedure from "add 6 ml of dipyridylglyoxal mono(2-pyridyl)hydrazone at 0.04% in ethanol..." to construct a calibration curve.

## Results and Discussion

*Recovery of cobalt in the presence of vitamins and hormones*

Several experiments were carried out to check that the presence of various vitamins and hormones (present in geriatric preparations) had no adverse effects on the recovery of cobalt.

In the first experiment, one drop of each of vitamins A, E and K were added to 0.25 ml of a 50 μg/ml standard cobalt solution and 10 ml of distilled water in a 150-ml separating funnel, and after thorough mixing the vitamins were extracted with 10 ml of methylisobuthylketone. After quiet setting, the aqueous layer containing the cobalt ion was removed into a 25-ml volumetric flask. A few millilitres of distilled water were added to the separating funnel in order to remove any remaining cobalt, shaking and collecting again the aqueous layer into the 25-ml volumetric flask. The cobalt was then determined as described under the recommended procedure.

In the second experiment, about 0.4 g of vitamin $B_1$, 0.1 g of vitamin $B_2$, 0.2 g of vitamin $B_6$ and 3 g of vitamin C were added to a 100-ml volumetric flask. 40 ml of ethanol and distilled water to the mark were then added. One ml of this suspension was transferred to a 25-ml volumetric flask, 0.25 ml of a standard solution of 50 μg/ml of cobalt was then added, and the recommended procedure was again applied.

In the third experiment; in a 25-ml volumetric flask, 1 ml of each of the following aqueous solutions, vitamin $B_6$ at 0.2% w/v, vitamin $B_1$ at 0.4% w/v, vitamin C at 3% w/v, vitamin $B_2$ saturated solution, and 1 ml of vitamin $D_3$ at 0.05% in ethanol were mixed with 0.25 ml of a 50 μg/ml standard cobalt solution, and the recommended procedure for the determination of cobalt was applied.

In the fourth experiment, 3.7 mg of testosterone, 25 mg of *p*-aminobenzoic acid, 3.2 mg of folic acid, 15.5 mg of nicotinamide and 12 mg of estradiol were added to a 25-ml volumetric flask, together with 0.25 ml of a solution of 50 μg/ml of cobalt, the recommended procedure being then applied.

Finally, the effect of relatively high cyanocobalamin (vitamin $B_{12}$) contents in the cobalt-colored reaction was also studied.

Results obtained (Table 1) indicated that there was no difference between the recorder response of these solutions and the result from a standard cobalt sample. However, it was found that a correction had to be made for colored material for samples II and IV which absorb to some extent at 510 nm. This was achieved by making analyses which were identical to that described, except that the dipyridylglyoxal mono(2-pyridyl)hydrazone was purposely omitted.

TABLE 1

*Recovery of cobalt in the presence of various vitamins, 12.5 μg Co added*

| Experiment | $A_{510}$ | Co (μg) | Recovery (%) |
|---|---|---|---|
| I | 0.250 | 12.39 | 99.1 |
| II * | 0.272, 0.274, 0.275, 0.022, 0.018, 0.018 (color blank) | 12.39, 12.72, 12,78 | 99.1, 101.8, 102.2 |
| III * | 0.245 | 12.11 | 96.9 |
| IV * | 0.245 | 12.11 | 96.9 |
| V | 0.252<br>0.007 (color blank) | 12.11 | 96.9 |

$A_{510}$ of a reference sample measured against distilled water = 0.252. $A_{510}$ of a reagent blank measured against distilled water = 0.028.

* Samples filtered before measurements

TABLE 2

*Composition of Hidropolivit Mineral (per tablet)*

| | | | |
|---|---|---|---|
| Vitamin A | 4000 I.U. | Cobalt sulphate | 0.05 mg |
| Vitamin $D_2$ | 500 I.U. | Magnesium oxide | 6 mg |
| Vitamin E | 1 mg | Phytic acid, magnesium salt | 0.88 mg |
| Vitamin $B_1$ | 2 mg | Calcium | 1.4 mg |
| Vitamin $B_2$ | 1 mg | Phosphorus | 2.2 mg |
| Vitamin $B_6$ | 1 mg | Iron oxalate | 2 mg |
| Vitamin $B_{12}$ | 20 μg | Zinc chloride | 0.5 mg |
| Vitamin C | 40 mg | Nickel sulphate | 0.1 mg |
| Vitamin K | 0.1 mg | Copper sulphate | 0.5 mg |
| Vitamin PP | 15 mg | Gold chloride | 0.01 mg |
| Calcium panthothenate | 2 mg | Molybdenum (ammonium molybdate) | 0.1 mg |
| Folic acid | 5 mg | Fluorine (potassium fluoride) | 0.01 mg |
| Orotic acid | 0.2 mg | Iodine (potassium iodide) | 0.01 mg |
| Hesperidin | 0.25 mg | Saccharin sodium salt | 1.6 mg |
| (+)-Biotin (Vitamin H) | 0.25 mg | Excipients | remainder |
| Manganese sulphate | 0.5 mg | | |

Materials used in pharmaceuticals such as starch, lactose, glucose, saccharin and glycine at high levels had no significant effect on the recovery of cobalt. The specificity of the method for the determination of cobalt in the presence of other minerals (Asuero et al., 1987), hormones, vitamins and excipients, even when they are present at levels many times those normally found in multivitaminic (Van den Eeckhout and Moerlose, 1972) and geriatric (Eldewy and Tawfik, 1976; Van den Eeckhout and Moerlose, 1972) preparations, has been clearly demonstrated.

*Determination of cobalt in Hidropolivit Mineral*

Hidropolivit Mineral has the composition per tablet indicated in Table 2. A least-squares treat-

TABLE 3

*Determination of cobalt in Hidropolivit Mineral*

| Method | mg Cobalt/tablet ($\bar{X} \pm$ S.D.) | | | $F_{\exp} = \frac{V_a}{V_b}$ | $t_{\exp} = \frac{\bar{X}_a - \bar{X}_b}{\text{S.D.}^*}$ |
|---|---|---|---|---|---|
| Dipyridylglyoxal mono(2-pyridyl)hydrazone (DMPH) | 0.027<br>(0.029 ± 0.003) | 0.033 | 0.028 | 3.44 | 1.58 |
| Biacetyl mono(2-pyridyl)hydrazone (BPH) | 0.027<br>(0.026 ± 0.002) | 0.024 | 0.027 | | |

$$\text{S.D.} = \sqrt{\frac{\sum (X - \bar{X})^2}{n - 1}}$$

$$V_t = \frac{\sum (X_a - \bar{X}_a)^2 + \sum (X_b - \bar{X}_b)^2}{(n_a - 1) + (n_b - 1)}$$

$$^* \text{ S.D.} = \sqrt{\frac{V_t}{n_a} + \frac{V_t}{n_b}}$$

Theoretical value of $F$ at 95% probability level = 19. Theoretical value of $t$ at 95% probability level = 2.776.

[a] 6.25 ml of BPH at 0.25% were used

ment of a calibration graph gave the following relationship between the absorbance ($y$) and the amount of cobalt in $\mu$g/ml ($x$); $y = 0.0053 + 0.4326\ x$. Triplicate absorbance values for sample (0.405, 0.419, 0.406), reagent blank (0.024, 0.024, 0.024) and color blank (0.307, 0.301, 0.306) gave a mean value ($\bar{x} \pm$ S.D.) for the cobalt content per tablet of 0.029 ± 0.003 mg.

For the purpose of this investigation, spectrophotometric estimation of the cobalt as the biacetyl mono(2-pyridyl)hydrazone complex (Asuero and Rodriguez, 1980) was chosen as the standard by which reliable comparative data could be obtained. From examination of the data of Table 3, it will be found that the mean values obtained in the two general procedures are in good agreement as shown by means of the $t$-test (Lacroix, 1962). Use was made of the $F$-test (Lacroix, 1962) to compare the precision of the two methods. Comparison of the variances showed that there was no significant difference in precision between them.

The data given by the manufacturer do not indicate if the salts added are hydrated or not. In any case, by assuming the cobalt salt added to be dehydrated, the amount of the cobalt content per tablet would be 0.019 mg, a value lower than the value found by us. Undoubtedly a mistake may be made in the label of the multivitaminic prepration which was purchased from the market. It has been suggested (Ali, 1984) that the amount of salt and the corresponding amount of trace element should be clearly defined and declared on the label of each multivitamin preparation. Although only the determination of cobalt in Hidropolivit Mineral has been described — by using a procedure in which preliminary ashing is eliminated — the method is appropriate to similar determinations in other pharmaceutical preparation.

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