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Determination of potassium in pharmaceutical formulations by means of 18-crown-6: extraction studies*

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Abstract: A colorimetric method has been developed for the determination of potassium in pharmaceutical formulations. The method is based on the formation of a complex of potassium with 18-crown-6, followed by conversion to an ion-pair with picrate anion; the ion-pair is extracted with either methylene chloride or toluene–methylene chloride (80:20, v/v) and determined colorimetrically.

Keywords: *Potassium assay in pharmaceuticals; potassium-18-crown-6 complex; potassium colorimetric determination; potassium complex extractive analysis.*

Introduction

The importance of potassium in the biological and pharmaceutical fields has been widely recognized [1, 2] as is apparent from the number of investigations devoted to metabolism, nutritional aspects and hypokalaemia, as well as to the drugs that can be used to correct potassium depletion (e.g. potassium-sparing diuretics). Variations in potassium content in intra- and extra-cellular fluids of the body can be tolerated only within restricted limits; for this reason it is necessary to be able to determine potassium accurately, especially in prolonged perfusional therapy designed to correct potassium deficiency. Thus there is a need for simple, highly specific, analytical methods for the quality control of potassium-containing pharmaceutical formulations and for the determination of potassium in biological fluids.

Methods based on atomic absorption spectroscopy [3], flame photometry [4] and ion-selective electrodes [5, 6] have been reported for the determination of potassium in pharmaceutical formulations. An alternative method based on visible and UV absorption spectroscopy forms the subject of the present communication. The method involves the formation of a potassium complex by mixing an aqueous solution of a potassium salt with a solution of 18-crown-6 in a suitable organic solvent. This complex is soluble in organic solvents and is stable, but it does not absorb in the visible range. However, it can be converted to an ion-pair by the addition of a large counter-ion that is

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highly polarizable and intensely coloured, such as picrate. The ion-pair thus formed ([18-crown-6]$^+$–picrate$^-$) is extracted with an organic solvent and determined colorimetrically.

This study forms part of an on-going investigation [7] and has the aim of extending and improving the method proposed. Various organic solvents have been studied in order to determine their extraction efficiency, the final choice of solvent being dictated by the need to combine high sensitivity and good reproducibility; both necessary prerequisites for the successful analytical application of the method.

Experimental

Apparatus

A double-beam spectrophotometer (Jasco, UVIDEC 610) and a single-beam spectrophotometer (Jasco, UVIDEC 4) were used. pH values were measured with a Crison model 501 pH-meter.

Materials

All chemicals were of analytical grade and were obtained from Carlo Erba (Italy); deionized and double-distilled water was used.

Stock solutions of 18-crown-6 (1,4,7,10,13,16-hexaoxacyclo-octadecane), potassium chloride and lithium picrate were 1×10^{-2}, 1×10^{-2} and 2×10^{-2} M, respectively, and were used to prepare standard solutions by appropriate dilution.

Procedure

To 2 ml of lithium picrate solution of the desired concentration in a centrifuge tube was added 2 ml of standard KCl solution. The pH of the solution was adjusted to 6.5–7.5 with Li_2CO_3 and treated with 4 ml of 18-crown-6 dissolved in the organic solvent investigated (1×10^{-2} M). After mechanically stirring for 4 min and centrifuging for 4 min, the organic phase was separated. A blank solution was prepared with distilled water in place of KCl solution.

Extraction studies. The residual aqueous phase of the various samples and that of the blank solution (to allow for potassium-independent picrate$^-$ extraction), was analysed colorimetrically. A calibration graph was constructed using standard aqueous solutions of lithium picrate, using absorbance values at 354 nm. This graph was linear for the concentration range 1×10^{-5}–1×10^{-4}M ($y = 14300x - 2.88 \times 10^{-3}$; $r = 0.9999$) and the values for the molar extinction coefficient were in good agreement with the literature value [8].

Determination of potassium in pharmaceutical formulations. The absorbance of the organic phase was measured at 369 nm for solvent I and 361 nm for solvent IV against a blank prepared in the same way. Under optimized experimental conditions, calibration curves were constructed for both solvents. Commercial preparations were powdered, diluted with water and subjected to the above procedure.

Results and Discussion

Of the various organic solvents tested for the extraction of the ion-pair, [K-18-crown-

6]$^+$–picrate$^-$, the following were studied in detail: chloroform, methylene chloride, isobutylmethylketone and toluene–methylene chloride (80:20, v/v).

Figure 1 shows the absorption spectra obtained from the organic phase after extracting the ion-pair. The spectra have a similar shape; they all show two bands in the visible region, the sharp peak with a λ_{max} of 360–380 nm and a shoulder near 420 nm. In order to verify which solvent gave the best extraction yield and the best reproducibility, tests were carried out on standard potassium solutions in the presence of picrate and an excess of the ligand [7].

Extraction studies

The quantity of potassium extracted was deduced from the difference between the known starting quantity of potassium and that remaining in the aqueous layer. The potassium content of the aqueous phase was first determined by atomic absorption spectrometry, but other methods were found to be superior in their reproducibility and were consequently selected, as explained below. On the assumptions [9] that the quantity of picrate anion extracted is equimolar with the [K-18-crown-6] complex and that within the complex the potassium–crown ratio is 1:1, the extracted quantity of picrate is a measure of the potassium extracted. As an analytical method for the picrate the

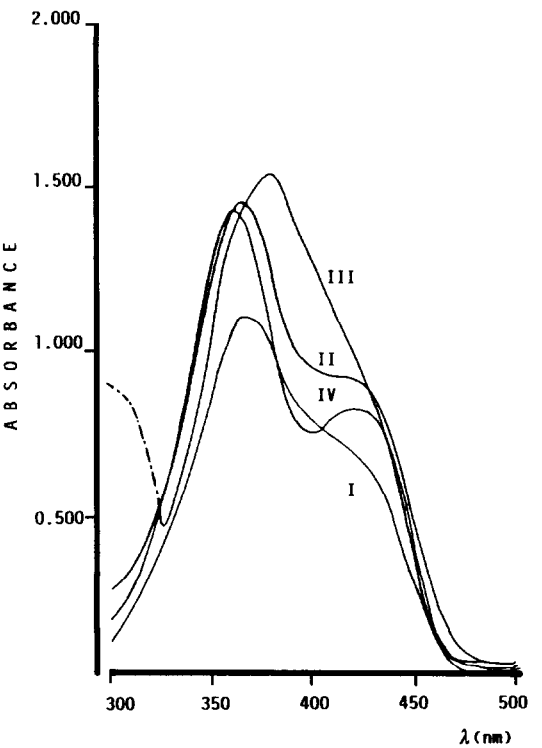

Figure 1
Absorption spectra of the ion-pair [K-18-crown-6]$^+$-picrate$^-$, obtained after extraction with the organic solvents: I, methylene chloride; II, chloroform; III, isobutylmethylketone; and IV, toluene–methylene chloride (80:20, v/v). Potassium solutions were at different concentrations in the presence of picrate$^-$ (2.5×10^{-4} M) and 18-crown-6 (1×10^{-2} M).

spectrophotometric determination [10] was chosen since it was faster and simpler than the polarographic technique recently proposed [11].

Indeed ion-pair extraction causes decreased absorption of the picrate ion in the aqueous phase; this difference enables the quantity of picrate which has migrated to the organic phase as the ion-pair and hence the quantity of the potassium complex extracted to be determined. It was found that a small fraction of free picrate was indeed extracted and the extraction values have all been corrected for this effect.

Influence of pH and picrate concentration

All solvents were found to give an optimum performance at pH 6.5–7.5; however, pH values lower than 6.5 caused an increase in free picrate extraction.

The influence of picrate concentration on extraction efficiency was studied in detail. Figure 2 shows the dependence of % extraction on picrate concentration (18-crown-6 and potassium concentrations were constant). It can be seen that all solvents show a similar trend; a rise followed by a levelling off of the curve.

Efficiency and reproducibility

The extraction efficiency in isobutylmethylketone was 42% for a picrate concentration of $\geq 2.5 \times 10^{-4}$ M. However, this high efficiency was counter-balanced by a high extraction of free picrate in the organic phase, which led to a reduction in the reproducibility of the determination of potassium.

Chloroform, on the other hand, although characterized by a good extraction efficiency (58% for a picrate concentration of 5×10^{-4} M) did not give good reproducibility because it randomly turned opaque during experiments.

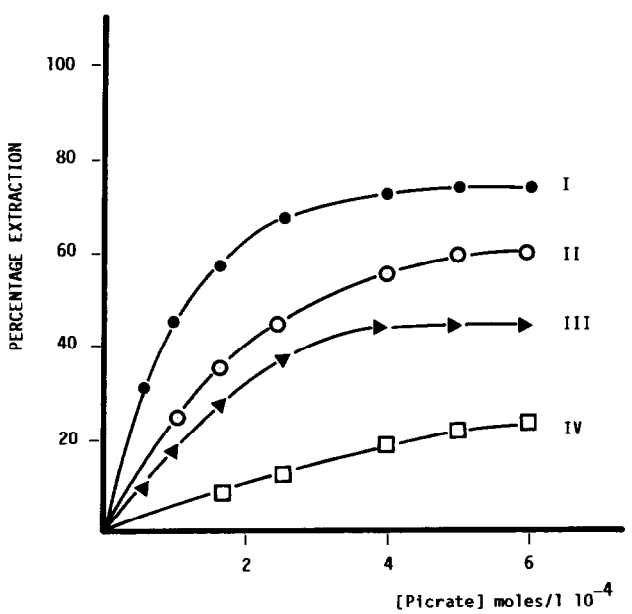

Figure 2
Influence of picrate$^-$ concentration on extraction efficiency (18-crown-6 and potassium at constant concentrations; 20°C). I, methylene chloride (●); II, chloroform (○); III, isobutylmethylketone (▲); and IV, toluene–methylene chloride (80:20, v/v) (□).

The solvent mixture, toluene–methylene chloride (80:20, v/v), did not give a high extraction yield (22% for a picrate concentration of 5×10^{-4} M) but nevertheless gave highly reproducible measurements. Finally, methylene chloride proved to be the solvent of highest extracting power (72% for a picrate concentration of 5×10^{-4} M); however, this solvent had to be used with caution for concentrations of picrate lower than 1×10^{-4} M, to avoid an increase in free picrate.

The efficiency of extraction followed the order: methylene chloride (I) > chloroform (II) > isobutylmethylketone (III) > toluene–methylene chloride (80:20, v/v) (IV); however, reproducible determinations, as required for analytical applications, could only be attained with (I) and (IV).

Potassium calibration curves

For I and IV, at constant concentrations of 18-crown-6 and picrate, the efficiency of extraction did not vary with potassium concentration. Consequently, solvents I and IV were selected for the colorimetric procedure based on formation of the ion-pair [K-18-crown-6]$^+$–picrate$^-$. The wavelength chosen was 369 nm for I and 361 nm for IV (see Fig. 1). The Beer–Lambert law was observed over the potassium concentration range 1.28×10^{-5}–1×10^{-4} M for I ($y = 7832x + 7.37 \times 10^{-3}$; $r = 0.9998$) and 5×10^{-5}–2.5×10^{-4} M for IV ($y = 2574x + 5.9 \times 10^{-3}$; $r = 0.9997$).

Stability studies

Tests of stability at 20°C showed that in solvent I the ion-pair [K-18-crown-6]$^+$–picrate$^-$ had a constant absorbance for at least 2 h, whereas for solvent IV the solution was stable for at least 24 h.

Analytical applications

Both solvents were used for the analysis of potassium in pharmaceutical formulations and showed good accuracy: 98.5–100.6% for I ($n = 6$) and 99.1–100.2% for IV ($n = 7$). Precision was also satisfactory: RSD = 0.9% for I ($n = 6$) and 0.8% for IV ($n = 7$).

Of course, owing to its greater sensitivity, solvent I would be preferred for the determination of trace amounts of potassium ($\leq$1 ppm) in pharmaceutical preparations or in biological fluids.

The accuracy of the procedure was assessed by recovery studies in the two solvents. Known volumes of KCl standard solution were added to a known amount of the pharmaceutical formulation and the recovery was evaluated by the procedures described: recovery = 99.0–100.4% for I ($n = 5$) and 99.3–100.2% for IV ($n = 5$); RSD = 0.8% for I ($n = 5$) and 0.7% for IV ($n = 5$). The accuracy of the colorimetric method was compared with that of a method based on the use of a potassium selective electrode [5]; very good agreement was obtained.

Conclusions

This colorimetric procedure, based on the selective formation of a complex of potassium with 18-crown-6 and on organic solvent extraction of the ion-pair formed by the complex cation and picrate anion, is suitable for the rapid and sensitive analysis of potassium in commercial formulations. For assays of acceptable accuracy and precision, either methylene chloride or toluene–methylene chloride (80:20, v/v) should be used as the solvent.

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