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Titrimetric determination of sulphate in pharmaceutical products

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A method is described for the titrimetric determination of sulphate in pharmaceutical products. After fixation of the base on a cation exchange resin column, sulphuric acid was titrated with barium chloride in the presence of thorin indicator. The titrimetric method was compared with the gravimetric method.

During the analysis of amine hydrochlorides or hydrobromides the halide content is often determined, whereas a similar assay of sulphate is rarely made. The principal reason probably is that the gravimetric method, which is rather elaborate, is still the best known method. During our study of methods of analysis of sulphates of basic antibiotics (Roets & Vanderhaeghe, 1966), a rapid method of assay of sulphate was needed.

Direct titration of sulphate can be made with lead nitrate or with a barium salt (Wilson & Wilson, 1960). The assay of sulphate with lead nitrate using dithizone has been described as a macromethod (Archer, 1957) and as a micromethod (Soep & Demoen, 1960). Another direct titration method uses barium chloride with sodium alizarin-3-sulphonate (Alizarin red S) or 1-(*o*-arsonophenylazo)-2-naphthol-3,6-disulphonic acid sodium salt (thorin) as indicator (Fritz & Freeland, 1954). This method has been adapted as a micromethod with barium perchlorate as reagent and thorin as indicator (Fritz & Yamamura, 1955; Wagner, 1957). This titration method now seems to be the most used method for the determination of sulphur after Schöniger combustion (Dominicus, 1968).

The titration of sulphate with barium must be made between pH 2·3 and 3·7 and it is necessary to add a quantity of alcohol sufficient to obtain a concentration of 30 to 40% to observe a precise end-point (Fritz & Freeland, 1954). We have found that it was impossible to apply this method for the analysis of sulphates of basic antibiotics, because the end-point was difficult to observe, owing to the formation of a precipitate upon addition of alcohol to the aqueous solution. This difficulty could be eliminated by fixation of the base on a cation exchange resin. This method has been applied previously for the removal of interfering mineral cations (Fritz & Freeland, 1954).

MATERIALS AND METHODS

Reagents

Magnesium acetate 0·2 M. Methanol pr. anal. Barium chloride 0·1 M, acidified with 60% perchloric acid to pH 3·0. The titre of this solution is determined with H_2SO_4 (0·1N), using the general method. Thorin: 0·025% solution in water. Methylene blue: 0·0125% solution in water.

Resin column

A chromatographic column of 20 cm height and 1·5 cm i.d. provided with a sintered-glass disk is used. A volume of 10 ml of Dowex 50-X4 or X8 (200–400 mesh, Analyti-

cal Grade) is introduced into the column, and is washed with 3·5N hydrochloric acid, followed by distilled water until no chloride reaction is observed in the eluate. The column can be used for several assays. The resin is regenerated by washing with 3·5N hydrochloric acid followed by distilled water until no chloride reaction is observed.

Method

About 200·0 mg of the sulphate salt, accurately weighed, is dissolved in 10 ml of water with moderate warming. This solution is put on the column, without disturbing the surface of the resin. The column is washed with distilled water (about 50 ml) until the eluate is neutral. After adjusting the pH of the eluate to about 3·0 with magnesium acetate, 40 ml of methanol is added. After addition of 5 drops of thorin and 1 drop of methylene blue, the solution is titrated with barium chloride 0·1M until the green colour changes to pink.

RESULTS

To examine the precision of the method, 10 determinations of the sulphate content of ammonium sulphate were performed. The standard deviation was 0·30, which gave a value of 72·56% with confidence limits (*P* 0·95) of ±0·22. The values of sulphate content of neomycin samples IV and V were 28·68 and 28·65% with confidence limits (*P* 0·95) of ±0·34 and ±0·17 for four assays.

The sulphate content of several pharmaceutical products was determined by the gravimetric (Vogel, 1961) and the titrimetric method. The results are given in Table 1. The values are averages of duplicate or quadruplicate determinations.

Table 1. *Determination of sulphate and loss on drying.*

	% Sulphate (SO_4)[a]			Loss on drying	
	Grav.	Titr.	Theor.	Found	Theor.
Neomycin sulphate					
Sample I	25·24	25·19	31·70[b]	7·11	—
II	26·27	26·16		5·63	
III	28·23	28·39		6·72	
IV	28·47	28·68		6·56	
V	28·98	28·65		7·06	
Streptomycin sulphate $(C_{21}H_{39}N_7O_{12})_2 \cdot 3H_2SO_4$	18·79	18·79	19·77	2·51[d]	—
Dihydrostreptomycin sulphate $(C_{21}H_{41}N_7O_{12})_2 \cdot 3H_2SO_4$	18·20	18·39	19·72	3·44[d]	
Colistin sulphate	16·37	16·40	16·96[c]	7·03[d]	
Isoprenaline sulphate $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4 \cdot 2H_2O$	17·17	17·22	17·23	n.d.[e]	6·46
Sparteine sulphate $C_{15}H_{26}N_2 \cdot H_2SO_4 \cdot 5H_2O$	22·85	22·71	22·73	20·70[f]	21·22
Quinidine sulphate $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$	12·30	12·35	12·27	4·61[g]	4·60
Atropine sulphate $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$	13·70	13·86	13·82	3·74[f]	2·58
8-Hydroxyquinoline sulphate $(C_9H_7NO)_2 \cdot H_2SO_4$	23·85	23·96	24·74	0·14[f]	0

a. Sulphate content of undried products.
b. Calculated for neomycin B or C sulphate, $C_{23}H_{46}N_6O_{13} \cdot 3H_2SO_4$.
c. Calculated for colistin A sulphate, $C_{53}H_{100}N_{16}O_{13} \cdot 2{\cdot}5H_2SO_4$.
d. Three h at 60° on phosphorus pentoxide at a pressure of 0·1 mm Hg.
e. Not done.
f. At 105°.
g. At 125°.

There is excellent correlation. The theoretical sulphate content given for neomycin sulphate is the value calculated for neomycin B or C sulphate. Neomycin, in fact, never contains that amount of sulphate because it would yield an acid sulphate, which is rather unstable in solution. Neomycin also contains other components besides neomycin B and C.

For other products the results correspond well with the expected values. The determination of the moisture content completes the analysis or permits a correction to the dried substance.

For the products examined, the degree of cross-linking of the resin was not critical; either Dowex 50-X8 or X4 could be used, with all the products except colistin sulphate, for which accurate results could not be obtained with Dowex 50-X8. The high degree of cross-linking of this resin probably prevents sufficient penetration of the polypeptide in the maze of the resin. For the analysis of colistin sulphate it is necessary to use Dowex 50-X4.

Elution of the resin with water yields a solution of sulphuric acid, which means that an acidimetric titration is possible. We have preferred a specific assay of sulphate with barium chloride in the presence of thorin, because a small amount of acid may be liberated by the resin and because the sulphate of the amine may contain other anions.

It may be concluded that the rapid titrimetric assay of sulphate could replace the gravimetric method in the analysis of several pharmaceutical products.

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