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FURTHER APPLICATIONS OF THERMOANALYTICAL METHODS TO THE DETECTION OF POTASSIUM AND SODIUM SALTS OF PENICILLINS AND CEPHALOSPORINS *

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ABSTRACT

The potassium and sodium salts of some penicillins and cephalosporins were analyzed by thermoanalytical techniques (TG, DTG and DSC); in particular, those antibiotics whose thermal decomposition in oxygen occurs too quickly. The analyses were carried out in atmospheres of static air and oxygen, with and without the addition of ammonium sulphate or ammonium persulphate. It is possible to evaluate the purity of these antibiotics from the resultant sodium or potassium sulphate residue. Better results in terms of accuracy and precision were obtained by the addition of ammonium sulphate or persulphate to the analyzed compounds.

INTRODUCTION

Previously [1,2] we have shown that it is possible to perform a purity control of sodium cephalosporins and penicillins by thermogravimetric analysis in an atmosphere of oxygen. The analysis was carried out by an indirect method based on the determination of sodium, as sodium sulphate, obtained as the residue of the thermogravimetric scan in the temperature range 20–850°C (addition of ammonium sulphate in the case of penicillins). In this work we describe the application of the same method to the determination of the potassium salts of the above antibiotics. Unfortunately, the experimental work was markedly limited by the poor number of these antibiotics commercially available. We have considered the modifications required in the case of those antibiotics whose thermal decomposition in an atmosphere of oxygen occurs too quickly, thus causing poor accuracy of the analysis. The addition

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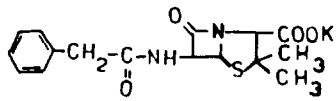
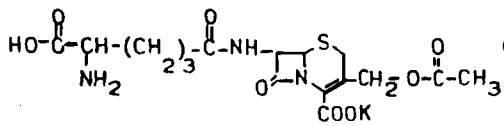
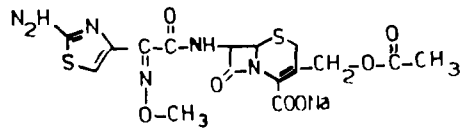
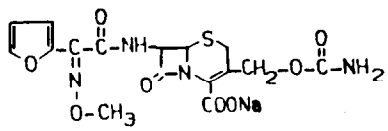
TABLE 1

Compounds examined

Antibiotic salt	Structural formula	Empirical formula	Mol. wt.
Potassium benzylpenicillin		$C_{16}H_{17}N_2KO_4S$	372.47
Potassium cephalosporin C		$C_{16}H_{20}N_3KO_8S$	453.51
Sodium cefotaxime		$C_{16}H_{16}N_5NaO_7S_2$	477.45
Sodium cefuroxime		$C_{16}H_{15}N_4NaO_8S$	446.37

of ammonium persulphate in the place of ammonium sulphate has been investigated. The formulae of the additional antibiotics studied in the present work are given in Table 1; those of the antibiotics studied previously are given elsewhere [1,2].

MATERIALS AND METHODS

Benzylpenicillin potassium salt and a drug containing potassium benzylpenicillin with 4.28% sodium citrate and 0.15% citric acid were supplied by Squibb S.p.a., cephalosporin C potassium salt by Sigma Chemical Company, cefotaxime sodium salt by Hoechst, and cefuroxime by Glaxo S.p.a. Ammonium sulphate and ammonium persulphate were Merck pro analysis.

The TG and DTG curves of the examined compounds were obtained using a DuPont model 951 thermobalance. The heating rate was 10°C min^{-1}, and the furnace atmosphere was oxygen at a flow rate of 100 ml min^{-1}, or static air. The DSC curves were obtained using a DuPont Model 990 DSC cell and console. The heating rate was 10°C min^{-1} with an atmosphere of oxygen at a flow rate of 100 ml min^{-1}. The flame photometric measurements were carried out by an Instrumentation Laboratory 243 flame photometer. The IR spectra were obtained using a Perkin-Elmer 177 IR spectrophotometer.

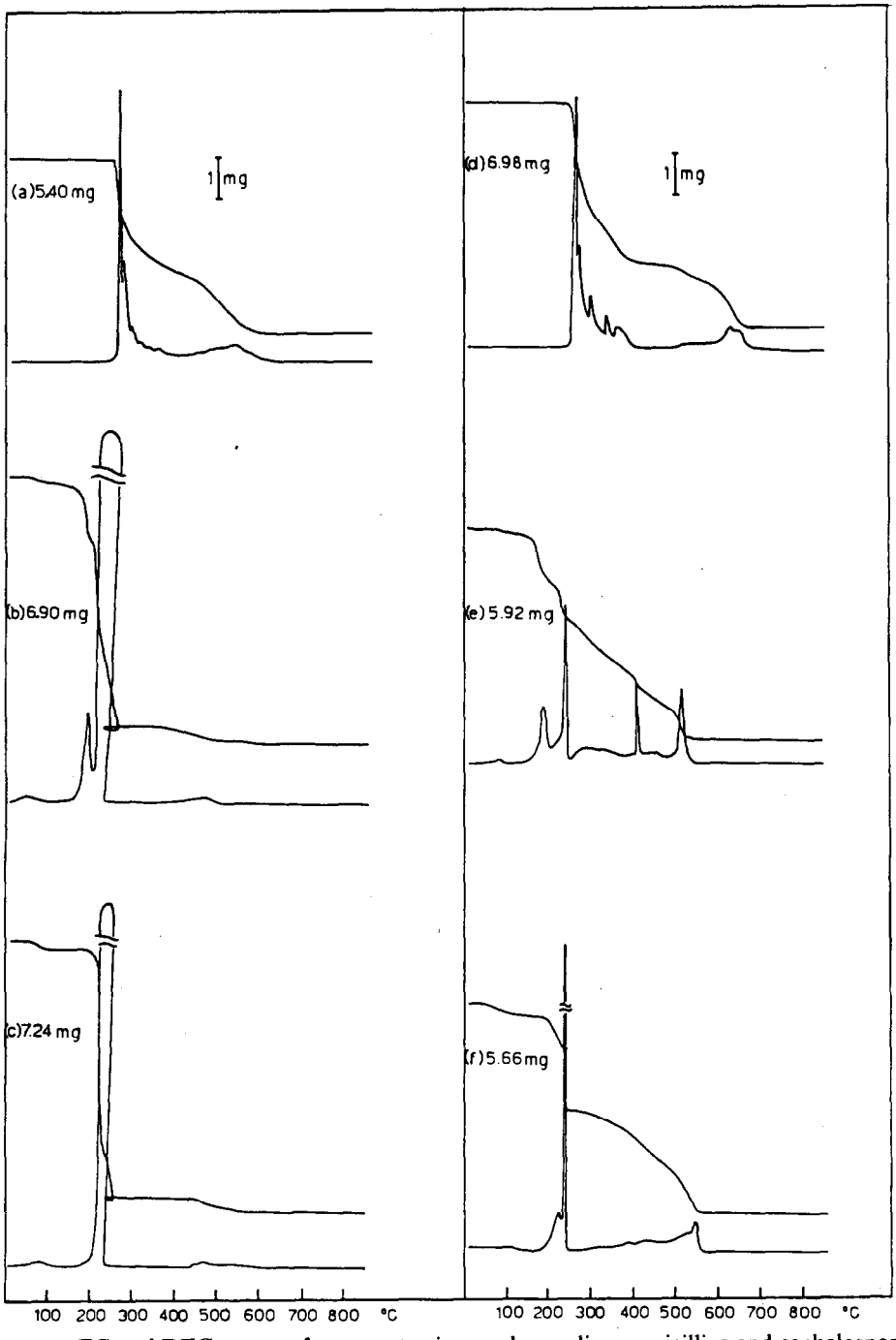


Fig. 1. TG and DTG curves of some potassium and or sodium penicillins and cephalosporins. Heating rate, 10°C min^{-1}; static air or oxygen at a flow rate of 100 ml min^{-1}. (a) Potassium benzylpenicillin, (b) potassium cephalosporin C, (c) sodium cefotaxime, in oxygen; (d) potassium benzylpenicillin, (e) potassium cephalosporin C, (f) sodium cefotaxime, in static air.

TABLE 2

Thermal analysis of the compounds in static air and in a stream of oxygen. The wt.% of the residues at the end of each process is referred to the anhydrous compound (water is expressed as a fraction of the anhydrous compound)

Antibiotic salt	H_2O loss		First processes			Second processes		
	Found (%)	pdt	Calcd. (%)	Found (%)	pdt	Calcd. (%)	Found (%)	pdt
Potassium benzylpenicillin								
in oxygen				47.4	240	23.4	23.0	420
					270			535
					420			670
static air				43.6	240	23.4	22.4	460
					265			620
					460			720
Potassium cephalosporin C								
in oxygen	2.3	25		15.1	140	19.2	9.2	350
		50			230			475
		90			350			600
static air	2.3	50		27.7	140	19.2	12.4	475
		80			245			515
		100			475			560
Sodium cefotaxime								
in oxygen	3.0	25		16.0	170	14.9	11.5	400
		80			240			470
		110			400			600
static air	3.6	35		58.0	180	14.9	14.5	265
		95			240			545
		130			265			580

RESULTS

The thermogravimetric analyses of potassium benzylpenicillin and potassium cephalosporin C were performed in oxygen and static air; these are the only commercially available salts of the antibiotics under consideration. The TG and DTG curves are shown in Fig. 1, and the corresponding TG data are summarized in Table 2. It is observed that the thermal decomposition of potassium benzylpenicillin in oxygen shows almost the same characteristic as the decomposition of the corresponding sodium antibiotic [2]: it begins at 240°C (230°C for sodium benzylpenicillin) and proceeds through two main processes. The first decomposition process, at the end of which the characteristic residue of potassium sulphate and carbon is obtained, ends at a temperature lower (420°C) than in the case of the sodium antibiotic (650°C); the second process, during which carbon is transformed into CO_2 and so only potassium sulphate is obtained as residue, occurs in only one step and is complete at 670°C, as compared with 820°C in the case of sodium benzylpenicillin. By comparing the curves of potassium benzylpenicillin performed in oxygen and in air, it is observed that although the behaviour is substantially the same, the steps in oxygen are sharper and the residue of sulphate is obtained at a lower temperature (670°C vs. 720°C in air). In the case of potassium cephalosporin C the curves in oxygen and in air are quite different. In oxygen there is a very fast first process, during which the decomposition of the full antibiotic is observed, followed by a second less evidenced process; in static air the decomposition is more gradual and the two processes of thermal demolition are little differentiated. By observing the thermal decomposition behaviour of potassium cephalosporin C in oxygen, it is found to be very similar to that of sodium cefuroxime studied previously [1], thus indicating such a violent decomposition in oxygen is not a characteristic peculiar to sodium cefuroxime. On this basis we investigated the possibility of some other cephalosporins exhibiting behaviour similar to that of the two examined ones: it was so evidenced that at least, among the commercially available cephalosporins, the sodium cefotaxime yields the same thermal decomposition curve. Also the thermogravimetric curves in oxygen and static air, performed for the sodium cefotaxime, are reported in Fig. 1 and the corresponding data are summarized in Table 2. For this antibiotic the same observations can be made as for cefuroxime and cephalosporin C. In particular, it can be observed that for all three antibiotics in oxygen the final residues are not quantitative and as evidenced previously [1], from this point of view better results are obtained by the tests in static air. Even if this really corresponds to quantitative results for cefuroxime and cefotaxime, in the case of cephalosporin C, also under these conditions, data still seem markedly inaccurate when compared with the potassium percentage calculated on the basis of the formula of Table 1; on the contrary these data are in good agreement with the results of flame photometric analysis.

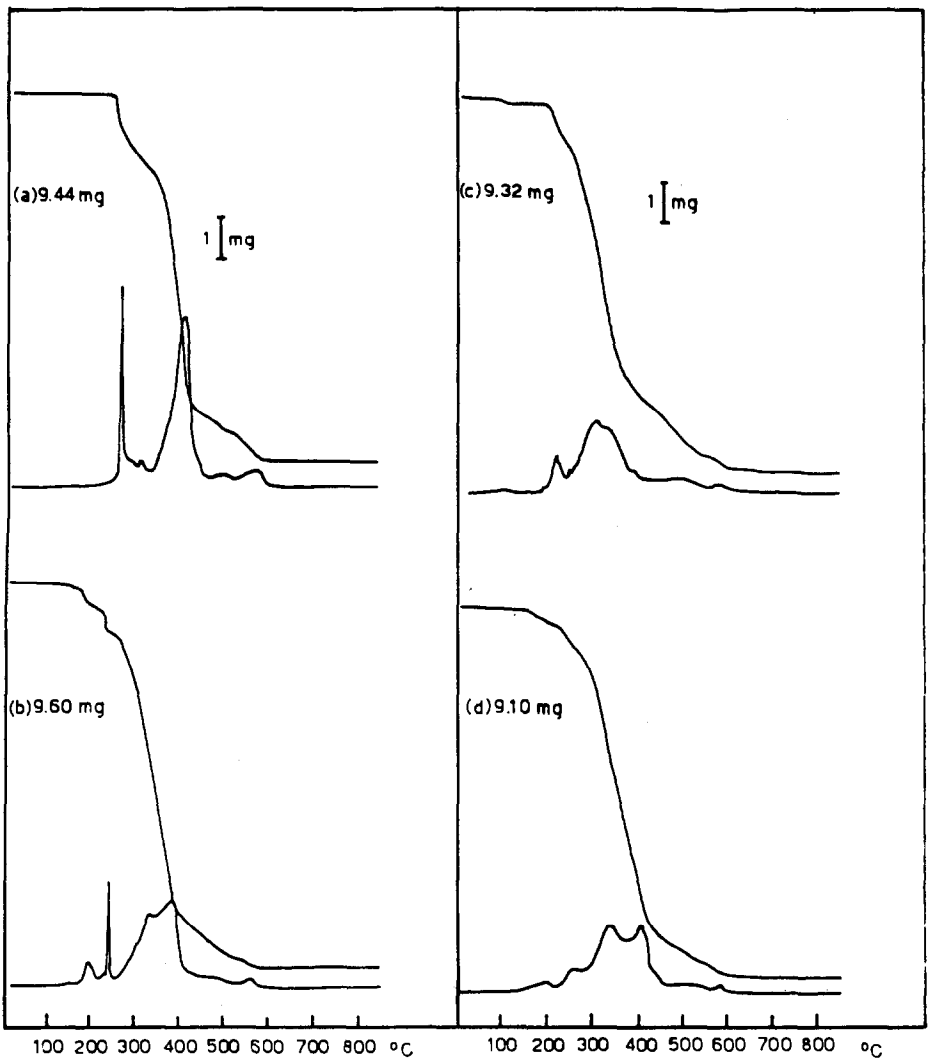


Fig. 2. TG and DTG curves of some potassium and sodium penicillins and cephalosporins with the addition of ammonium sulphate (AS), in a stream of oxygen at a flow rate of 100 ml min^{-1}; heating rate, 10°C min^{-1}. (a) Potassium benzylpenicillin with 61.3% (w/w) AS, (b) potassium cephalosporin C with 51.5% (w/w) AS, (c) sodium cefotaxime with 50.6% (w/w) AS, (d) sodium cefuroxime with 66.6% (w/w) AS.

On the basis of the good results obtained by the addition of ammonium sulphate in the analysis of sodium penicillins, when non-quantitatively satisfying results were obtained [2], we tried the addition of this salt, finely minced, to the antibiotics studied in this paper. The thermogravimetric curves obtained in oxygen with the addition of known amounts of ammonium sulphate are shown in Fig. 2. Table 3 summarizes the results obtained for the analysis of the sodium or potassium content by TG, in

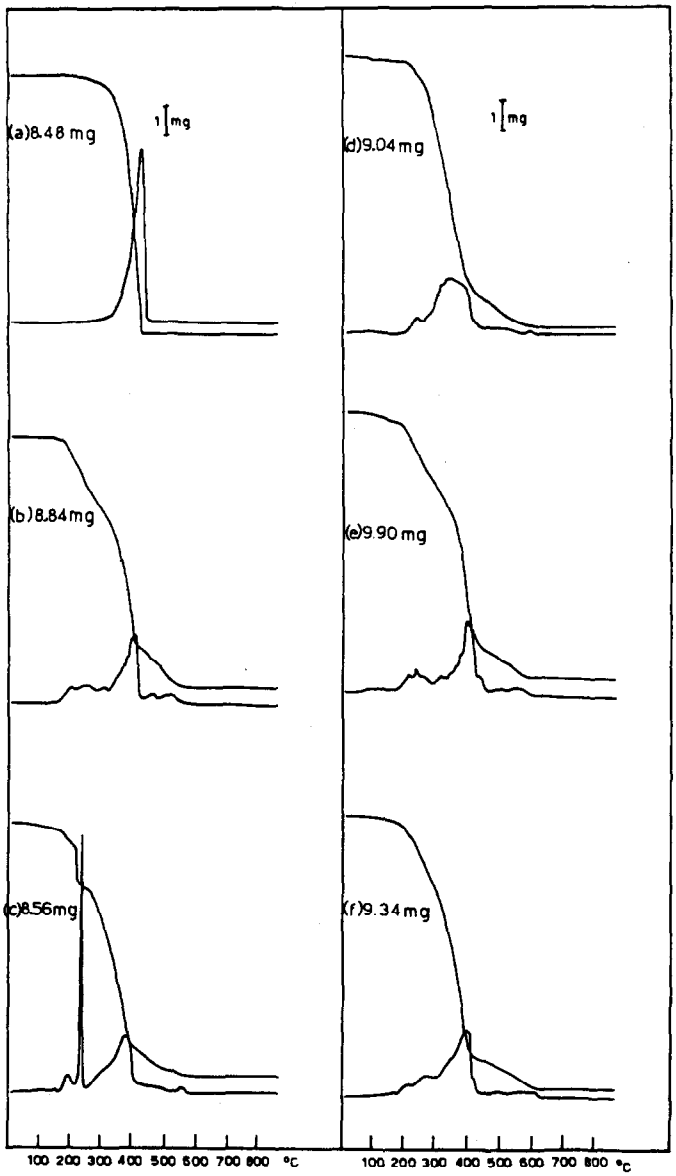


Fig. 3. TG and DTG curves of ammonium persulphate (AP) and some potassium or sodium penicillins and cephalosporins with the addition of ammonium persulphate, in a stream of oxygen at a flow rate of 100 ml min^{-1}; heating rate, 10°C min^{-1}. (a) Ammonium persulphate, (b) potassium benzylpenicillin with 63.2% (w/w) AP, (c) potassium cephalosporin C with 53.8% (w/w) AP, (d) sodium cefotaxime with 67.3% (w/w) AP, (e) sodium carbenicillin with 61.6% (w/w) AP, (f) sodium methicillin with 69.6% (w/w) AP.

TABLE 3

Potassium and sodium contents of the compounds examined: comparison of the results obtained by TG in static air, and oxygen, with and without the addition of ammonium sulphate, and flame photometry (values are the means of three determinations)

Antibiotic salt	% K calcd.	% K found by TG (static air)	% K found by TG (in oxygen)	% K found by TG (in oxygen; with AS added)	% K found by flame photometry	% Difference between found and cald. values			
						TG (static air)	TG (oxygen)	TG (oxygen with AS added)	Flame photometry
Potassium benzylpenicillin	10.50	10.03	10.31	10.56	10.63	−4.5	−1.8	+0.6	+1.2
Potassium cephalosporin C	8.62	5.57	4.13	5.79	5.86	−35.4 (−4.9) [a]	−52.1 (−29.5) [a]	−32.8 (−1.2) [a]	−32.0

	%(K + Na) calcd.	%(K + Na) found by TG (static air)	%(K + Na) found by TG (in oxygen	%(K + Na) found by TG (in oxygen with AS added)	%(K + Na) found by flame photometry				
Potassium benzylpenicillin with 4.28% sodium citrate and 0.15% citric acid	11.7	10.11	10.13	11.18	11.13	−9.5	−9.3	+0.1	−0.4
	% Na calcd. 1.14				% Na found 1.18				+3.5
	% K calcd. 10.03				% K found 9.95				−0.8
	% Na calcd.	% Na found by TG (static air)	% Na found by TG (in oxygen)	% Na found by TG (in oxygen) with AS added)	% Na found by flame photometry				
Sodium cefotaxime	4.82	4.69	3.72	4.79	4.64	−2.7	−22.8	−0.6	−3.7
Sodium cefuroxime	5.16	5.06	4.51	5.13	5.37	−1.9	−12.6	+0.6	+4.1

% AS = Ammonium sulphate.

[a] % Difference between value found by flame photometry and by TG, in static air, and in oxygen with and without AS added.

TABLE 4

Sodium content of the compounds examined, obtained by the addition of ammonium persulphate, in a stream of oxygen (values are the means of three determinations)

Antibiotic salt	% K calcd.	% K found by TG with AP added (in oxygen)	% Difference between found and calcd. value
Potassium benzylpenicillin	10.50	10.50	0.0
Potassium cephalosporin C	8.62 (5.86) [a]	5.97 5.97	−30.7 (+1.9) [b]
	%(K + Na) calcd.	%(K + Na) found by TG with AP added (in oxygen)	
Potassium benzylpenicillin with 4.28% sodium citrate and 0.15% citric acid	11.17	11.20	+0.3
	% Na calcd.	% Na found by TG with AP added (in oxygen)	
Sodium cephotaxime	4.82	4.81	−0.2
Sodium cefuroxime	5.16	5.15	−0.2
Sodium cephalothin	5.49	5.49	0.0
Sodium cephapirin	5.15	5.14	−0.2
Sodium carbenicillin	10.89	10.91	+0.2
Sodium methicillin	5.71	5.69	−0.4

AP = Ammonium persulphate.

[a] Values found by flame photometry.

[b] % Difference between value found by flame photometry and by TG with AP added.

static air, in an atmosphere of oxygen, with and without the addition of ammonium sulphate, and by flame photometry, for the antibiotics under examination. As observed from the experimental results (Table 3), the addition of ammonium sulphate allows quantitative analysis to be performed also for sodium and potassium cephalosporins with decomposition processes which occur too quickly; for potassium cephalosporin C only, the potassium content determination yields a value lower than the calculated one, which is

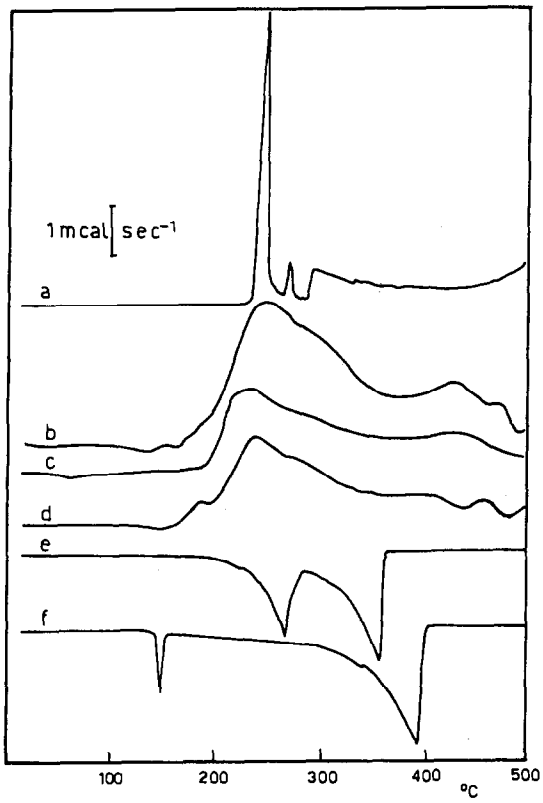


Fig. 4. DSC curves of some potassium and sodium penicillins and cephalosporins and ammonium sulphate and ammonium persulphate, in a stream of oxygen at a flow rate of 100 ml min^{-1}; heating rate, 10°C min^{-1}. (a) Potassium benzylpenicillin, (b) potassium cephalosporin C, (c) sodium cefotaxime, (d) sodium cefuroxime, (e) ammonium sulphate, (f) ammonium persulphate.

still in good agreement with the corresponding data of flame photometric analysis.

By observing the temperature values of the thermogravimetric curves of sodium and potassium cephalosporins and of the other cephalosporins previously examined, it can be pointed out that for all these antibiotics the decomposition processes begin at temperatures lower than for penicillins, generally between 135 and 170°C for the former, and between 160 and 240°C for the latter; only in this second case is the temperature not so far from the decomposition melting point of ammonium sulphate (235°C) [3]. It is better if the added salt has a melting point possibly lower, or at least near to that one of the start of decomposition of the antibiotic which can then be closely mixed with the molten salt before decomposition occurs. Ammonium persulphate is characterized by properties similar to those of sulphate: the presence of sulphur atoms in the molecule, full decomposition, without

residue, above 430°C (see thermogram in Fig. 3) and a lower melting point (120°C) [3]. The thermogravimetric analysis in oxygen with the addition of known amounts of ammonium persulphate, dried and finely minced, was performed for all the sodium and potassium cephalosporins and penicillins listed in Table 3, but also for other cephalosporins and penicillins examined previously, the thermogravimetric analyses of which, if performed without any addition, were scarcely quantitative. Some of the obtained thermogravimetric curves are reported in Fig. 3. Table 4 summarizes the results for the analysis of the sodium and potassium contents, by TG, in oxygen atmosphere, with known amounts of added ammonium persulphate for all the examined antibiotics.

The compositions of the residues of the thermal decomposition processes, particularly the residual sodium or potassium sulphate, were controlled by the same techniques (IR, chemical analysis) described previously [1,2]. The DSC curves in oxygen between 25 and 500°C for all the antibiotics reported in Table 1 are shown in Fig. 4. These curves can be useful for qualitative analysis, but not for quantitative analysis as no well-defined isolated peaks useful for quantitative purposes can be evidenced, probably with the only exception of potassium benzylpenicillin. Also, no evident melting process is present in these curves. In this temperature range, which corresponds to that of the first decomposition process in the TG curves, a continuous succession of exothermal reactions is observed. The calorimetric curves in oxygen of ammonium sulphate and persulphate are also shown in Fig. 4. The marked temperature difference between the two endothermal melting peaks is evident; of course the read temperature values are procedural temperatures.

CONCLUSIONS

Even if the number of the examined potassium antibiotics is poor, the thermogravimetric curves of Fig. 1 show a very similar trend for the corresponding potassium and sodium salts. Particularly the thermogravimetric curves of potassium benzylpenicillin show that for this antibiotic the curves in oxygen yield the best results; nevertheless, Tables 3 and 4 show that for pure benzylpenicillin practically quantitative data are always obtained both in oxygen and in static air and with the addition of ammonium sulphate of persulphate. The same is not observed when penicillin is contained in commercial drugs with other compounds such as citric acid and sodium citrate; in these cases, in agreement with previous studies [2], quantitative data are only obtained in the presence of ammonium sulphate or persulphate when it is possible to calculate the total amount of sodium and potassium contained in the examined drug. The comparison with flame photometry (Table 3), by which less accurate data are obtained than by thermogravimetric method [1], indicates that in this case photometry has the

advantage of yielding separately sodium and potassium content in the drug; but the total (sodium + potassium) content, on the basis of photometric analysis, is less accurate than the thermogravimetric data.

The thermogravimetric and photometric data (Tables 3 and 4) obtained for potassium cephalosporin C clearly suggest that in this case the potassium content in the antibiotic is lower than that of the calculated value, if the salt is considered pure. This can be explained if the purity grade of the analyzed product is considered: really it is not analytically pure grade, but practical grade (about 85%, as nominal value yielded from producer). In this case it is more significant to compare thermogravimetric data with photometric data, rather than with the calculated value in which case good agreement is observed (Tables 3 and 4).

Concerning the analysis of the antibiotics, such as cefuroxime, cefotaxime and cephalosporin C (three examined among 18 in this and previous work), which decompose too quickly in oxygen, it can be concluded (Fig. 1, Table 3) that data obtained in oxygen and without any addition of salt are not quantitative. Thermogravimetric analysis in static air yields better but not fully satisfactory results. On the contrary, thermogravimetric analysis performed by the addition of ammonium sulphate yields quantitative residues of sodium sulphate for these antibiotics also. Quantitative data are also obtained, for these and several other antibiotics, by the addition of ammonium persulphate, as clearly shown by the results in Table 4. It can thus be concluded that the addition of ammonium persulphate is theoretically advantageous over that of the sulphate both for the lower melting point and for the higher sulphur% content. Experimentally, for the examined antibiotics, both the salts yielded good results, not markedly different for precision, as % standard deviation always $\leqslant 4\%$, and for inaccuracy (± 1–2%) relative to the nominal values. Regarding the reproducibility of the tests in the absence of ammonium salt additions, it was found to be of about 4% for potassium benzylpenicillin in oxygen and static air, but much lower for the other antibiotics reported in Table 1, for which also the accuracy, under these experimental conditions, was found to be too low for the purpose of analysis.

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