Use of Cerium(IV) Sulphate in the Spectrophotometric Determination of Paracetamol in Pharmaceutical Preparations

Salah M. Sultan, Ibrahim Z. Alzamil, Abdullah M. Aziz Alrahman, Saad A. Altamrah and Yousif Asha
Chemistry Department, College of Science, King Saud University, Riyadh 11451, P.O. Box 2455, Saudi Arabia

An accurate spectrophotometric method is proposed for the determination of paracetamol. Cerium(IV) sulphate is used to oxidise paracetamol in 5 M H_2SO_4 to *p*-benzoquinone, which is then determined at 410 nm. The method has been successfully applied to the analysis of commercial pharmaceutical preparations and the results have been statistically compared with those obtained by the official (BP) method.

Keywords: *Pharmaceutical preparations; cerium(IV) sulphate; paracetamol determination; sulphuric acid; spectrophotometry*

Paracetamol (*N*-acetyl-*p*-aminophenol) is well known as an analgesic anti-pyretic drug. Many methods for its determination have been described, including titrimetry,[1–7] chromatography,[8–24] electrochemistry[25–27] and spectrophotometry.[28–41] In the official method (BP),[1] paracetamol is determined titrimetrically with cerium(IV) in acidic media using 1,10-phenanthroline - iron(II) complex (ferroin) to determine the end-point. The titration is performed in ice.

In the present method, cerium(IV) was reacted for 90 min with paracetamol in concentrated sulphuric acid in a water-bath maintained at 80 °C. The final product of the oxidation of paracetamol, *p*-benzoquinone, was spectrophotometrically determined at the wavelength of its maximum absorption (410 nm). This method was applied to the determination of paracetamol in drugs used for the treatment of coughs, colds and influenza.

Experimental

Apparatus

A Beckman Model 35 spectrophotometer connected to a Beckman Model 24–25 ACC recorder was used for all absorbance measurements. Matched sets of W 210/UU 10.00 mm cells were used throughout.

Reagents and Samples

Quartz-processed high-purity distilled water was used throughout. All chemicals and reagents were of analytical-reagent or pharmaceutical grade.

Paracetamol (pure form). This was prepared in our laboratory by acetylation of *p*-aminophenol.[42] The purity of the crystalline powder was checked by melting-point, IR and NMR techniques. The stock solution from this compound (1 mg ml^{-1}) was prepared by dissolving exactly about 1 g in warm water, stirring for 10 min and diluting to 1 l in a calibrated flask after cooling. The absolute purity of this material was 99.81% as determined by the official method[1] and it complied with the BP specifications.

Paracetamol (tablets). Ten tablets were weighed and ground into a fine powder. A mass of powder containing about 500 mg of paracetamol was weighed accurately, mixed with about 150 ml of water, warmed and stirred for 10 min. This was then filtered through a Whatman No. 41 filter-paper, washed with water and then the filtrate plus washings were diluted to 500 ml with water in a calibrated flask after cooling.

Paracetamol (capsules). The contents of 10 capsules were carefully mixed and weighed. An amount equivalent to 500 mg of paracetamol was accurately weighed and dissolved in 150 ml of water, warmed and stirred for 10 min. The insoluble mass was filtered through a Whatman No. 41 filter-paper and washed with water. The filtrate and washings were transferred into a 500-ml calibrated flask and diluted to volume after cooling to room temperature.

Cerium(IV) solution. A stock solution of $Ce(SO_4)_2$ (20 mg ml^{-1}) was prepared in 10 M sulphuric acid.

Sulphuric acid. A stock solution of 10 M was prepared in the usual way.

Procedure

A 4.00-ml volume of cerium(IV) sulphate solution was placed in a 50-ml calibrated flask to which 21.00 ml of sulphuric acid stock solution and the appropriate amount of paracetamol solution were added. The flask and contents were swirled, placed in a water-bath at a temperature maintained at 80 °C for 90 min, cooled under a tap and then diluted to the mark with water. The coloured product was determined at 410 nm against a reagent blank.

Results and Discussion

Kinetics

This method was based on the oxidation reaction of paracetamol with cerium(IV) in sulphuric acid media. The brown - red species determined at a $\lambda_{max.}$ of 410 nm was believed to be *p*-benzoquinone, the final product of paracetamol oxidation. This maximum was the only one obtained for the absorption spectra run in the range 300–750 nm. It was observed that the reaction was dependent on the concentration of sulphuric acid, and that the reaction only takes place at acid concentrations greater than 2 M. The rate of the reaction accelerated as the acid concentration was increased and slowed as the concentration decreased. At higher concentrations of sulphuric acid the redox potential of $Ce(SO_4)_2$ is such that it can be oxidised. This indicates that the de-acetylation of paracetamol to *p*-aminophenol is the rate-determining step. *p*-Aminophenol is then further oxidised with Ce(IV) to *p*-benzoquinone. This mechanism is similar to that recently proposed[2] for the oxidation of paracetamol using iron(III) as a one-electron oxidant in 8 M H_2SO_4.

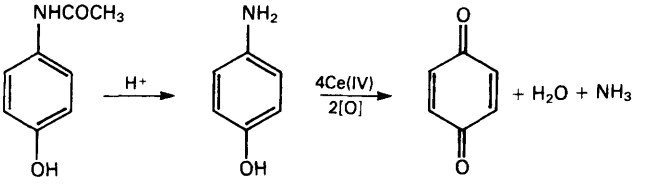

Table 1. Results of the determination of paracetamol in pure form and in pharmaceutical preparations compared with the official method.[1] Nos. 2–11 were in tablet form and 12 in capsule form

No.	Drug proprietary name (supplier)	Composition/mg	Recovery* ± standard deviation, % Proposed method	Official method (BP)[1]	Correlation† coefficient*[2]	$t_{calc.}$‡
1	Paracetamol (laboratory made)	99.81% paracetamol (absolute)	100.83 ± 0.27	100.80 ± 0.22	1.0000	0.28
2	Panadol (Winthrop, UK)	500 paracetamol	99.84 ± 0.53	100.50 ± 0.18	1.0002	1.04
3	Paracetamol (Smith, France)	500 paracetamol	99.84 ± 0.53	100.11 ± 0.10	1.0006	0.99
4	Revanin (Arab Pharmaceutical Manuf. Co., Jordan)	500 paracetamol	98.98 ± 0.16	99.11 ± 0.17	1.0010	0.67
5	Sinutab (Warner, UK)	300 paracetamol 25 phenylpropanolamine. HCl 22 phenyltoloxamine	98.58 ± 0.62	99.02 ± 0.14	0.9993	0.88
6	Revacod (Arab Pharmaceutical Manuf. Co., Jordan)	500 paracetamol 10 codeine phosphate	99.43 ± 0.30	99.65 ± 0.11	1.00	0.87
7	Triatussic (Wander, Switzerland)	200 paracetamol 5 mepyramine. HCl 4.2 pheniramine. HCl 12.5 phenylpropanolamine. HCl 20 noscapine 13 caffeine 90 terpin hydrate	100.21 ± 0.91	100.28 ± 0.25	0.99	0.69
8	Trimedil (Zyma, Switzerland)	100 paracetamol 0.25 dimetindene maleate 15 *o*-(β-hydroxyethyl)-rutoside 40 ascorbic acid 1.25 phenylephrine.HCl	185.51 ± 0.72	134.33 ± 0.23	—	—
9	Efferalgan (Upsa, France)	330 paracetamol 200 ascorbic acid	133.5 ± 0.49	140.48 ± 0.15	—	—
10	Prontopyrin (Mack, FRG)	200 paracetamol 250 aluminium acetylsalicylate 50 caffeine	110.58 ± 0.56	—	—	—
11	Veganin (Warner, UK)	250 paracetamol 250 acetylsalicylic acid 6.8 codeine phosphate	123.89 ± 0.49	—	—	—
12	Neopyrin-N (Knoll, FRG)	200 paracetamol 200 ethenzamide 10.72 isometheptene mucate 14.28 octamylamine mucate	98.64 ± 0.61	98.32 ± 0.14	1.0008	1.28

* Average of five determinations, assay as a percentage of label claim.
† For five determinations at different concentrations in the range 40–160 μg ml^{-1}.
‡ Theoretical value 2.78 (p = 0.05).

The reaction rate accelerated at elevated temperatures; 80 °C was found to be suitable to study the interference of other drug constituents without fear of chemical changes.

When the reactants in 5 M H_2SO_4 were left in the water-bath at 80 °C, the absorbance of the product at 410 nm increased with time. The reaction product attained maximum absorbance within 75 min and was found to be stable for 24 h at room temperature. Measurements taken earlier than 75 min were meaningless and rendered inaccurate results, and hence 90 min was found to be suitable for all experiments.

Analytical Data

Beer's law was valid over the concentration range between 30 and 160 μg ml^{-1}. Although the range was small, the results were accurate and were not affected at common dose levels. The linearity of concentration *versus* absorbance was calculated using a computer and the correlation coefficient was found to be 0.9967 with an intercept of 0.0781. The molar absorptivity, calculated from the slope, was found to be 811.21 l mol^{-1} cm^{-1}.

Precision

The method was applied to the determination of paracetamol in its pure form and in a number of pharmaceutical preparations. The results obtained (Table 1) seemed to be highly accurate and the method was successfully applied to the determination of paracetamol in the presence of excipients such as lactose, glucose and starch, which are usually added during the preparation of tablets and capsules. The presence of codeines, caffeines, noscapine, terpins, phenylephrines, phenylpropanolamine, phenyltoloxamine, mepyramine, pheniramine, dimethindene maleate, rutosides, isometheptene mucate, octamylamine mucate and ethenzamide together with paracetamol in drug formulations did not interfere with the results. However, the presence of ascorbic acid and acetylsalicylic acid in Efferalgan and Trimedil tablets and in Prontopyrin and Veganin tablets, respectively, showed positive interferences. In the determination of paracetamol in Prontopyrin and Veganin tablets by the official method,[1] the interference caused by acetylsalicylates made it impossible to determine the end-point of the titration.

The results of this method were compared with the results obtained by the official method[1] using the batch of samples presented in Table 1. The calculated *t*-values at the 95% confidence level did not exceed the theoretical value, indicating no significant difference between the two methods. However, this method is regarded as being superior to the official method[1] because it can be used for the determination of trace amounts of paracetamol whereas the official method[1] is titrimetric and cannot be applied accurately to trace analysis.

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References

1. "British Pharmacopeia 1980," HM Stationery Office, London, 1980, p. 326.
2. Srivastava, M. K., Ahmed, S., Singh, D., and Shukla, I. C., *Analyst,* 1985, **110**, 735.
3. Mohmoud, S. A., and Abdel, S. F., *Pharmazie,* 1979, **34**, 569.
4. Kalinowska, Z. E., and Hasztar, H., *Farm. Pol.,* 1976, **23**, 447.
5. Walash, M. I., Agarwal, S. P., and Martin, M. I., *Can. J. Pharm. Sci.,* 1972, **7**, 123.
6. Agarwal, S. P., and Walash, M. I., *Indian J. Pharm.,* 1974, **36**, 47.
7. Inamdar, M. C., Saboo, J. C., Kamdar, C. N., and Sanghavi, N. M., *Indian J. Pharm.,* 1973, **35**, 187.
8. Carnevale, L., *J. Pharm. Sci.,* 1983, **72**, 196.
9. Beckett, A. H., and Wilkinson, G. R., *J. Pharm. Pharmacol., Suppl.,* 1965, **17**, 104S.
10. Wallo, E. W., and d'Adamo, A., *J. Pharm. Sci.,* 1982, **71**, 1115.
11. Brochmann-Hanssen, E., and Svendsen, A. B., *J. Pharm. Sci.,* 1962, **51**, 1096.
12. Barnhart, J. W., and Caldwell, W. J., *J. Chromatogr.,* 1977, **130**, 243.
13. Plakogiannis, F. M., and Saad, A. M., *J. Pharm. Sci.,* 1977, **66**, 604.
14. Chao, M. K., Holcomb, I. J., and Fusari, S. A., *J. Pharm. Sci.,* 1979, **68**, 1463.
15. Kubiak, E. J., and Munson, J. W., *J. Pharm. Sci.,* 1980, **69**, 152.
16. Menyharth, A., Mahn, F. P., and Heveran, J. E., *J. Pharm. Sci.,* 1974, **63**, 430.
17. Sena, F. J., Piechocki, J. T., and Li, K. L., *J. Pharm. Sci.,* 1979, **68**, 1465.
18. Soni, S. K., and Dugar, S. M., *J. Forensic Sci.,* 1979, **24**, 437.
19. Das Gupta, V., *J. Pharm. Sci.,* 1980, **69**, 110.
20. Burke, D., and Sokoloff, H., *J. Pharm. Sci.,* 1980, **69**, 138.
21. McSharry, W. O., and Savage, I. V. E., *J. Pharm. Sci.,* 1980, **69**, 212.
22. Ko, C. Y., Marziani, F. C., and Janicki, C. A., *J. Pharm. Sci.,* 1980, **69**, 1081.
23. Townley, E., and Roden, P., *J. Pharm. Sci.,* 1980, **69**, 523.
24. Munson, J. W., and Kubiak, E. J., *Anal. Lett.,* 1980, **13(B8)**, 705.
25. Miner, D. J., Rice, J. R., Riggin, R. M., and Kissinger, P. T., *Anal. Chem.,* 1981, **53**, 2258.
26. Jollow, D. J., Thorgeirsson, S. S., Potter, W. Z., Hashimito, M., and Mitchell, J. R., *Pharmacology,* 1974, **12**, 251.
27. Miner, D. J., and Kissinger, P. T., *Biochem. Pharmacol.,* 1979, **28**, 3285.
28. Verma, K. K., Gulati, A. K., Palod, S., and Tyagi, P., *Analyst,* 1985, **109**, 735.
29. D'Souza, A. A., and Shenoy, K. G., *Can. J. Pharm. Sci.,* 1974, **36**, 47.
30. Kalatzis, E., and Zarbi, I., *J. Pharm. Sci.,* 1976, **65**, 71.
31. Inamdar, M. C., Gore, M. S., and Bhide, R. V., *Indian J. Pharm.,* 1974, **36**, 7.
32. Ellock, C. T., and Fogg, A. G., *Analyst,* 1975, **100**, 16.
33. Davis, D. R., Fogg, A. G., Burns, D. T., and Wragg, J. S., *Analyst,* 1974, **99**, 12.
34. Belal, S. F., Elsayed, M. A. H., Elwalily, A., and Abdine, H., *Analyst,* 1979, **104**, 919.
35. Elsayed, M. A. H., Belal, S. F., Elwalily, A., and Abdine, H., *Analyst,* 1979, **104**, 620.
36. Wallace, J., *Anal. Chem.,* 1967, **39**, 531.
37. Elsayed, N., Belal, S. F., Abdel, F. M., and Abdine, N., *J. Assoc. Off. Anal. Chem.,* 1979, **62**, 549.
38. Plakogianis, F. M., and Saad, A. M., *J. Pharm. Sci.,* 1975, **64**, 1547.
39. Mouton, M., and Masson, M., *Ann. Pharm. Fr.,* 1960, **18**, 759.
40. Welch, R. M., and Conney, A. H., *Clin. Chem.,* 1965, **11**, 1064.
41. Vaughn, J. B., *J. Pharm. Sci.,* 1969, **58**, 469.
42. Vogel, A. I., "Elementary Practical Organic Chemistry, Part 1," Longmans, London, 1958, p. 242.

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