Gas Chromatographic Analysis of Acetylsalicylic Acid, Acetophenetidin, and Caffeine Mixture in Pharmaceutical Tablet Formulations

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THE WIDESPREAD use of APC mixtures suggested the possibility that the technique of gas chromatography might be useful as an analytical method. Although it was felt that the chemically dissimilar natures of the ingredients and the widely differing quantities of drug mixtures in tablet formulations might present a problem, a single-run type of analysis was attempted. The results are reported below.

EXPERIMENTAL

Equipment.—A linear programed-temperature gas chromatograph, F & M Scientific Corp. model 609, equipped with a flame ionization detector, was used for the experimental work. The detector signal was supplied to a model Y153 Minneapolis-Honeywell 1-mv. recorder, with a 1-second full scale response and a chart speed of 20 inches per hour. A Disc Chart Integrator model No. 201B (Disc Instrument, Inc., Santa Ana, California) accessory to the recorder was also used. For injection a 10-μl.-capacity Hamilton syringe was employed.

Materials.—Helium (Matheson Co.) was used as carrier gas. Haloport F 60–80 mesh (a dispersion polymer of a tetrafluoroethylene obtainable from F & M Scientific Corp., Avondale, Pa.) was coated with 2% by weight of Dow Corning 200 Fluid, and packed into a 6-ft. stainless-steel column, 4 mm. I.D., with the aid of a vibrating motor shaft. The chemical materials used in the investigation were purchased from commercial sources.

Operating Conditions.—The column temperature was programed, in all cases, from 75 to 200°. The heating rate found optimal was 9° per minute. The flow rate of helium was maintained at 50 ml./min. ±3% when the inlet pressure was kept at 50 psig. This constancy was essential for quantitative results. The sample injection port was maintained at 325°, and the detector block at 275° was employed for all experiments. Division of the peaks was performed vertically at the minima or by the inside tangent method, and peak areas were estimated by use of the automatic integrator. Two-microliter injections of chloroformic solutions were used throughout.

Quantitative Analysis.—Internal normalization, using correction factors for the conversion of peak areas to weight composition, was employed. Synthetic APC mixtures of the same percentage composition found in commercial tablets were prepared (see Table I). Correction factors were obtained by dividing the calculated weight per cent of each component of interest by its corresponding peak area per cent. Sample mixtures were then analyzed by multiplying the peak area of each component by the corresponding correction factor. The corrected peak areas were then normalized in the usual procedure. A sample of the procedure is given in Table I (top).

Tablet A consisted of a commercial APC tablet, uncoated, containing no other active ingredients, and of the composition indicated. The ground equivalent of four tablets was placed into a 100-ml. volumetric flask and diluted to the mark with chloroform. The mixture was then stirred magnetically for 1 hour and filtered through a No. 42 Whatman paper. Ten milliliters of the filtrate was evaporated to dryness in a current of dry air at about 40 to 45°. The residue was taken up in exactly 2 ml. of chloroform. Two microliters of this solution was injected to yield a chromatogram of the form shown in Fig. 1.

Tablet B consisted of a commercial APC tablet that also contained chlorpheniramine maleate. Results are shown in Table I (lower portion).

A commercial tablet, containing 8.1 mg. of codeine phosphate per tablet in addition to an APC mixture of the same weight per cent composition as Tablets A and B, was analyzed by this procedure. The chromatograms were in every way identical to those of the other tablets and to the synthetic mixture, indicating that codeine does not interfere under the conditions employed. Some quantitative results are shown in Table I under Tablet C.

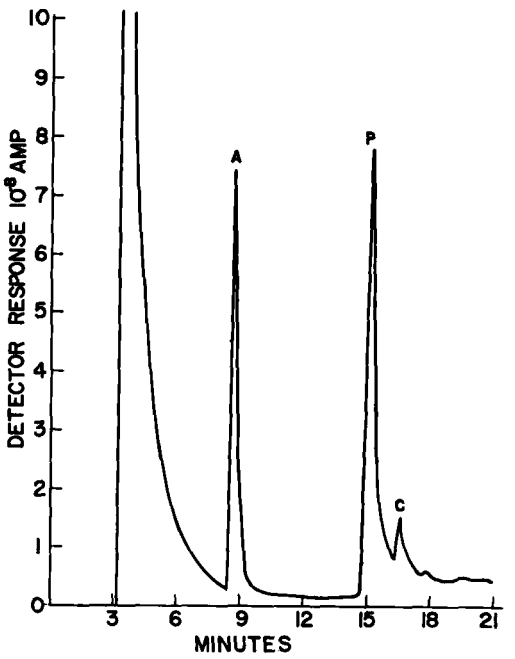

Fig. 1.—Typical gas chromatographic recording obtained for acetylsalicylic acid, acetophenetidin, and caffeine mixture with Dow Corning 200 fluid on Haloport F. Range 1000. Attenuation × 4.

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TABLE I.—PRECISION AND ACCURACY ANALYSIS OF A SYNTHETIC APC MIXTURE

	Component	Composition by Synthesis, % by Wt.	Run 1	Run 2	Run 3	Run 4	Mean	Av. Deviation from Mean, %	Av. Error, %
Synthetic mixture	Acetylsalicylic acid	53.52	53.31	55.06	54.33	54.75	54.36	±0.6	+1.6
	Acetophenetidin	38.34	38.36	37.12	37.74	37.96	37.79	−1.0	−1.4
	Caffeine	7.65	8.31	7.81	7.92	7.28	7.83	±3.6	+2.3
			Tablet Assays						
	Component	Labeled Composition, mg.	Run 1, mg.	Run 2, mg.	Run 3, mg.	Run 4, mg.	Run 5, mg.	Run 6, mg.	Mean, mg.
Tablet A	Acetylsalicylic acid	226.8	223.53	216.14	221.56	235.10	221.17	222.10	223.14
	Acetophenetidin	162.0	168.35	172.61	167.92	162.66	166.29	166.92	167.45
	Caffeine	32.4	32.4	32.4	31.72	31.34	33.70	32.10	32.28
Tablet B	Acetylsalicylic acid	226.8	224.64	217.04	226.36	227.70	225.23	...	224.19
	Acetophenetidin	162.0	161.78	170.21	161.48	160.00	162.16	...	163.11
	Caffeine	32.4	34.75	33.87	33.28	33.45	33.78	...	33.85
Tablet C	Acetylsalicylic	226.8	217.36	218.29	224.14	...	...	...	219.92
	Acetophenetidin	162.0	169.30	169.61	165.35	...	...	...	168.09
	Caffeine	32.4	33.98	32.77	31.17	...	...	...	32.64

SUMMARY AND DISCUSSION

GLC has been investigated with respect to its applicability to dosage forms containing APC mixture. It was felt that (*vis-a-vis* the N.F. column chromatographic technique) a method might be developed that would permit a greater number of replicate samples to be assayed, obviate the need for daily preparation of uniform columns, and release spectrophotometric facilities for other use.

This paper reports preliminary findings *via* a single-run type of assay. The results indicate that while the reliability of a single assay is less than in the official method, the means of the runs performed yielded results close to either labeled claim or composition by synthesis.

Efforts are being made to increase the precision of the technique and results will be reported in a future paper.

Communications

Possible Error in the Use of Polynomial Approximations in Urinary Excretion Rate Studies

Sir:

The utilization of urinary excretion data for the estimation of absorption rates has been employed in several reported studies (1–3). These papers indicate the method has certain advantages over one which bases its calculations on the concentration of the drug in blood plasma. Even though direct determination of plasma concentration of drug is recognized as a more accurate procedure, urinary excretion data are frequently employed since samples may be obtained at greater frequencies with a minimum of inconvenience to the subject, and drug concentration is such as to preclude assay difficulties.

Theoretical considerations of urinary excretion kinetics as related to absorption rate are reflected in the equation

$$dAe/dt = KfA_b$$

where dAe/dt is the rate of drug excretion; $K = 0.693/t_{1/2}$ where $t_{1/2}$ is the half-life of the drug in the body; f is the fraction of drug which is excreted in the urine unchanged; and A_b is the amount of drug in the body fluids. This equation is valid when the drug in the plasma is in equilibrium with other tissues and fluids of distribution. On the basis of this direct proportionality between excretion rate and the amount of drug in the body fluids, it is apparent that measurements of excretion rates plotted against time are far more indicative of rate of drug absorption than are plots of cumulative amounts of drug in the urine *vs.* time.

Excretion rates are defined as the instantaneous rate of change, at any given time, of cumulative