Determination of Acetylsalicylic Acid, Salicylamide, Acetaminophen, and Caffeine in Tablets or Powders by Independent Methods

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A method, suitable for automation, has been developed for the determination of four compounds commonly found in analgesic tablets. The tablet is dissolved in 85 percent methanol, filtered to remove the insoluble excipients, and three portions are taken. The first portion is analyzed for aspirin (ASA) by titration; the second portion, for acetaminophen (APAP) and salicylamide (SAL) by UV differential spectrophotometry; and the third portion for caffeine (CAF), either by a unique differential spectrophotometric operation, or by an extraction method, where the caffeine content is determined spectrophotometrically in the UV range. The average relative errors for each of the components are: 0.22% for aspirin, 0.51% for salicylamide, 0.80% for acetaminophen, 2.02% for caffeine by method I, and 1.18% for caffeine by method II.

THE ANALYSIS of a multicomponent system of analgesics usually requires many multiple separation steps or complicated UV, IR, or NMR methods, which demand solution of many simultaneous algebraic equations. Column chromatography (1) is a common procedure for the separation of phenacetin, caffeine, and acetylsalicylic acid. Solvent extraction methods for separation of components are described (2, 3). Other methods for determining the various components involve infrared spectrophotometry (4, 9), ultraviolet spectrophotometry (5, 6), titration (2), phosphorimetry (7), and nuclear magnetic resonance spectroscopy (8). Salicylic acid, acetylsalicylic acid, salicylamide, caffeine, and phenacetin in tablets or powders can be analyzed by spectrophotometric determination, requiring the solution of several algebraic expressions (10). Independent methods of analyzing for the constituents in a multicomponent system give greater accuracy, precision, and less computational problems than those which require the solution of simultaneous equations (11).

Recently, work from this laboratory has shown the power of the pH chromophoric procedure for the assay of drugs (12–14). Utilizing this concept, a method has been developed which can independently determine each of the four subject components of a tablet or powder, with no interferences from one another. It is not necessary to separate the components, except in the alternate method for caffeine, where just a simple chloroform extraction is performed. The procedures are very simple, rapid, accurate, precise, and can be easily automated.

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EXPERIMENTAL

Apparatus and Reagents

Spectrophotometer—A Beckman DU spectrophotometer was used for obtaining quantitative data for SAL, APAP, and CAF. A Beckman DK 2 recording spectrophotometer was used to obtain the spectra in Figs. 5 and 6.

Standard 1-cm. square fused silica cells were employed in all cases.

Titration Apparatus—Experimental data were obtained with a Beckman model No. 1019 research pH meter set to read the millivolt scale, with a Beckman standard combination electrode filled with saturated aqueous KCl solution.

Solvents—Spectral grade, analytical reagent methanol and chloroform (Merck Co.) were used. The solvent system, 85% methanol, was prepared by volume-volume dilution of anhydrous methanol with distilled, deionized water. The titration system was 0.5 *N* alcoholic potassium hydroxide from Hartman-Leddon Co., diluted with 85% methanol and standardized with potassium acid phthalate to be 0.02 *N*.

Buffer Solutions—(*a*) pH 1.3; 250 ml. of 0.2 *M* KCl, 336 ml. of 0.2 *M* HCl, and diluted to 1,000 ml. with distilled water.

(*b*) pH 6; 250 ml. of 0.2 *M* KH_2PO_4, 28 ml. of 0.2 *M* NaOH, and diluted to 1,000 ml. with distilled water.

(*c*) pH 10; 250 ml. of 0.2 *M* H_3BO_3, 250 ml. of 0.2 *M* KCl, 220 ml. of 0.2 *M* NaOH and diluted to 1,000 ml. with distilled water. (In all cases, reagent grade materials were used.) All analgesic compounds *i.e.*, acetylsalicylic acid, USP grade; salicylamide, NF grade; acetaminophen, NF grade; caffeine, USP grade, were checked for purity by infrared spectrophotometry.

Tablets—The standard composition of the synthetic tablets which were analyzed contained 195 mg. of aspirin, 130 mg. of salicylamide, 98 mg. of acetaminophen, and 65 mg. of caffeine.

PROCEDURE

The tablet to be analyzed is crushed to a powder, quantitatively transferred to a 100-ml. volumetric flask, and approximately 4 ml. of chloroform is added (to dissolve the CAF). The solution is brought to volume with 85% methanol, shaken to dissolve all the soluble materials, and filtered to remove the insoluble excipients (Solution *A*). From Solution *A*, a 20-ml. aliquot is transferred into a 250-ml. beaker (Solution *B*), a 4-ml. aliquot is transferred into a 200-ml. volumetric flask (Solution *C*), and a 5-ml. aliquot is transferred into a 200-ml. volumetric flask (Solution *D*).

Acetylsalicylic Acid (ASA)—To determine the ASA content, 100 ml. of 85% methanol is added to Solution *B* and a magnetic stirrer is placed in the beaker. Using 0.02 *N* alcoholic KOH, which has been standardized against potassium acid phthalate, the ASA is titrated potentiometrically with a standard combination electrode filled with saturated aqueous KCl solution. As an alternate procedure, the solution could be titrated to an orange-red end point in the presence of chlorophenol red indicator. (Most tablets containing ASA also contain small quantities of salicylic acid, which are negligible when compared with the amount of ASA present. Since salicylic acid is also titratable by this procedure, the analysis cannot be carried out in the presence of appreciable amounts of salicylic acid.)

Salicylamide (SAL) and Acetaminophen (APAP)—To determine the amounts of APAP and SAL, 5 ml. of 0.5 *M* NaOH is added to Solution *C*; the solution is allowed to stand for approximately 5 min. (to ensure complete conversion of ASA to its sodium salt), and then brought to volume with distilled water. A 20-ml. aliquot of this solution is transferred into each of two beakers. To one beaker, 10 ml. of pH 6 buffer is added, and to the other, 10 ml. of pH 10 buffer is added. Using the pH 6 buffer solution as the reference, and the pH 10 solution in the sample position, absorbance readings are taken on a DU spectrophotometer at 330 mμ (for SAL) and 263.5 mμ (for APAP).

Caffeine (CAF)—*Method I*—To determine the amount of CAF in the tablet, Solution *D* is brought to volume with distilled water, and a 20-ml. aliquot of this solution is pipeted into each of two beakers. To one beaker, 10 ml. of pH 1.3 buffer are added, and to the other, 10 ml. of 1:10 concentrated HCl:H_2O solution. An absorbance measurement is made on a DU spectrophotometer at 283 mμ, with the HCl solution in the reference position.

Method II—An alternate procedure for the determination of the CAF content is to bring Solution *D* to volume with 0.01 *M* NaOH, transfer a 30-ml. aliquot of this solution into a 250-ml. separator, and extract twice with 10-ml. aliquots of spectrograde chloroform. The chloroform extract is collected in a 50-ml. volumetric flask and brought to volume with the same solvent. The absorbance of this chloroform solution is read on a DU spectrophotometer at 276 mμ with chloroform as the reference solution.

RESULTS

Acetylsalicylic Acid (ASA)—Seven synthetic tablets, which contained varied amounts of ASA in the presence of standard amounts of CAF (65 mg.), APAP (98 mg.), and SAL (130 mg.), were titrated for ASA with extremely good results.

Salicylamide (SAL)—Figure 1 depicts three curves of absorbance readings at 330 mμ of solutions containing SAL alone, SAL in the presence of varying amounts of APAP, and SAL in the presence of standard amounts of ASA, CAF, and APAP. Since the three lines representing the relationships of the points coincide, it can be concluded that the determination of SAL in the tablets or powders is independent of the concentrations of the other ingredients, and therefore, no correction term needs to be applied in the calculations. By regression analysis the absorptivity for SAL at 330 mμ has been determined to be 36.5 absorbance units/(g./l.).

Acetaminophen (APAP)—Figure 2 depicts three curves of absorbance readings at 263.5 mμ of solutions containing various concentrations of APAP alone, APAP in the presence of varying amounts of SAL, and APAP in the presence of standard amounts of ASA, CAF, and SAL. Since the three lines representing the relationships of the points coincide, it may again be concluded that the determination of APAP in the tablets is independent of the concentrations of the other ingredients. The absorptivity for APAP at 263.5 mμ, as determined by regression analysis is 38.6 absorbance units/(g./l.).

Caffeine (CAF)—*Method I (Differential Spectro-*

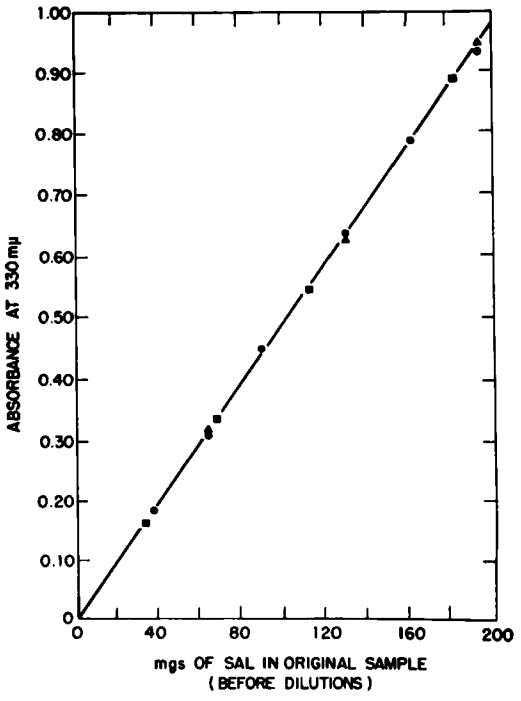


Fig. 1—Differential absorbances of various concentrations of SAL. Key: ■, SAL alone; ▲, SAL in the presence of varying amounts of APAP; ●, SAL in the presence of standard amounts of APAP, CAF, and ASA.

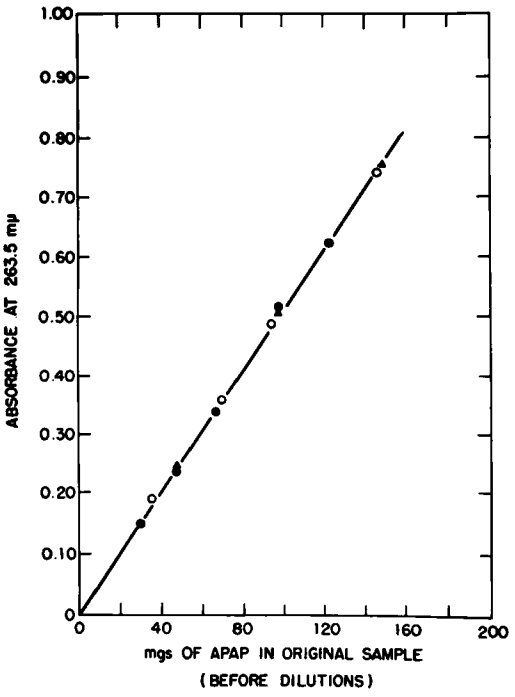


Fig. 2—Differential absorbances of various concentrations of APAP at 263.5 mμ. Key: ○, APAP alone; ▲, APAP in the presence of varying amounts of SAL; ●, APAP in the presence of standard amounts of SAL, ASA, and CAF.

photometry)—Figure 3 summarizes a number of experiments that were performed to determine whether there is any interaction between any of the components in this procedure. Absorbances at 283 mμ are plotted for: (*a*) various levels of CAF alone, (*b*) CAF in the presence of SAL, (*c*) CAF in the presence of APAP, (*d*) CAF in the presence of ASA, and (*e*) CAF in the presence of all three components. As can be seen, curves 1 through 4 are linear and coincide, proving that there is no interaction. The absorbance readings for CAF in the presence of all three components are linear to the 85-mg. region (mg. in the original sample); above this quantity the plot deviates from linearity. This observation may be explained in the following manner. Direct spectrophotometry, where water is used as the reference solvent, indicates that the sample solution containing 65 mg. of CAF plus standard amounts of the other components, reads about 1.2 in absorbance. At 130 mg., the reading is approximately 2.0. At this high absorbance, the phototube response to the small amount of light transmitted through the solution becomes nonlinear. Therefore, due to the high background absorbance of the other three components, readings above 0.125 are unreliable. At 283 mμ, the absorptivity for CAF, as determined by regression analysis, is 8.98 absorbance units/(g./l.).

Method II (*Extraction*)—Figure 4 represents the following relationships: (*a*) absorbances of various concentrations of CAF in chloroform, and (*b*) absorbances of various concentrations of CAF extracted into chloroform from standard amounts of ASA, APAP, and SAL. In both cases the same

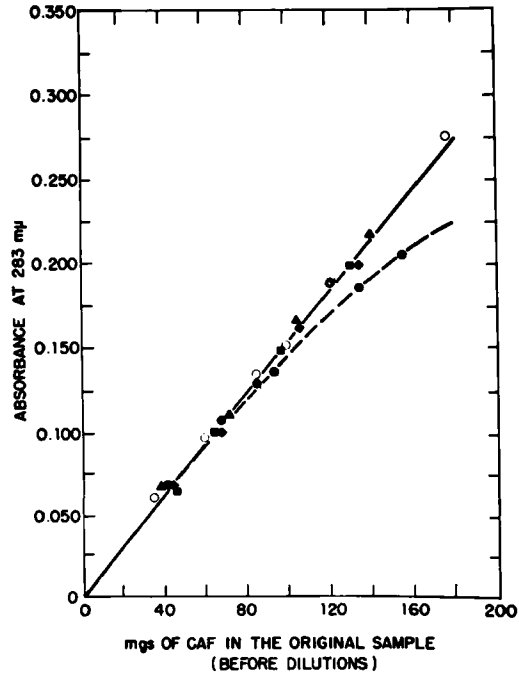


Fig. 3—Differential absorbances of various concentrations of CAF at 283 mμ. Key: ○, CAF alone; ▲, CAF in the presence of SAL; ■, CAF in the presence of APAP; ◆, CAF in the presence of ASA; ●, CAF in the presence of standard amounts of ASA, APAP, and SAL.

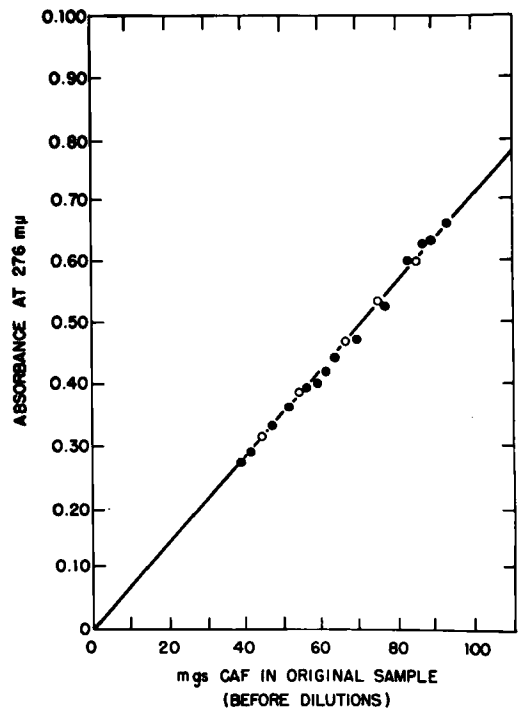


Fig. 4—Standard calibration curve for CAF in chloroform. Key: ○, CAF dissolved in $CHCl_3$; ●, CAF extracted into $CHCl_3$ from standard amounts of ASA, APAP, and SAL.

TABLE I—STATISTICAL RESULTS FOR EACH PROCEDURE

	No. Observations	No. of Analysts	Average Relative Error	Standard Deviation	95% Confidence Limits	95% Confidence Limits, mg.
ASA	7	1	0.22%	±0.30%	±0.60%	195 ± 1.15
SAL	18	4	0.51%	±0.84%	±1.68%	130 ± 2.18
APAP	18	4	0.80%	±1.00%	±2.00%	98 ± 1.96
CAF (method I)	18	4	2.02%	±2.41%	±4.82%	65 ± 3.13
CAF (method II)	24	3	1.18%	±1.43%	±2.86%	65 ± 1.86

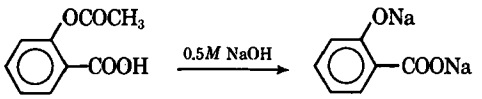
dilutions were made as described in the procedure, thus yielding the same final concentrations; however, for the sake of simplicity, the absorbances are plotted for mg. of caffeine in the original sample. By regression analysis, the absorptivity of CAF in chloroform at 276 mμ has been calculated to be 47.4 absorbance units/(g./l.), with a correction term of 0.013. The CAF concentration, therefore, is calculated using the following relationship: $(A_{276} + 0.013)/47.4$ = g. of CAF/l.

The statistical results for each of the procedures are summarized in Table I.

DISCUSSION

ASA is the only ingredient in the 85% alcoholic solution that is titratable (assuming that the amount of salicylic acid present is negligible). The excipients of the tablet or powder have no effect. For automation, spectrophotometric titration would be more workable than potentiometric titration. At the end point, a rapid color change of the dye indicator could be detected with a colorimeter or spectrophotometer.

In the SAL and APAP procedure, the ASA in the sample is converted to the disodium salt of salicylic acid with 0.5 *M* sodium hydroxide (15). See Scheme I.



Scheme I

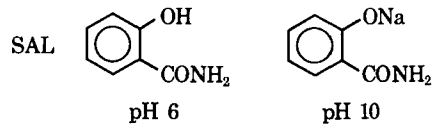
Since the pKa_1 and pKa_2 of salicylic acid are 3.0 and 13.4 (16), respectively, in buffers pH 6 and pH 10, the disodium salicylate converts to the monosodium salt (Scheme II):

Scheme II

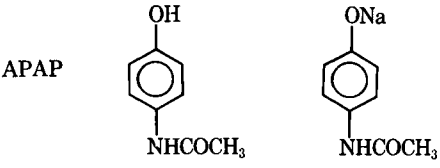
Consequently, since equal amounts of sample are contained in both buffered solutions, the absorbances of the two solutions due to ASA (which has been converted to monosodium salicylate) will exactly cancel each other, and the net absorbance will be zero.

The CAF (pKa = 13.39) (16) is in the same form at both pH's. The predominant species of APAP (pKa = 9.0) (16) and SAL (pKa = 8.4) (16) at the two different pH's are as in Schemes III and IV.

Therefore, at these two pH's each compound will exhibit different absorbance spectra. Consequently, since the pH 6 solution is in the reference position and the pH 10 solution is in the sample position, the spectra will automatically subtract in the spectrophotometer, giving new characteristic spectra for APAP and SAL.



Scheme III



Scheme IV

Figure 5 depicts the Beckman DK 2 differential spectra of samples containing various concentrations of SAL alone, APAP alone, and only CAF plus ASA. The samples were prepared by treating the individual components by the procedure described for SAL and APAP. The composition of the reference and sample solutions are as follows:

Reference pH 6	Sample pH 10	Absorbance 330 mμ	Absorbance 263.5 mμ
Monosodium salicylate (equivalent to ASA) + CAF	Monosodium salicylate (equivalent to ASA) + CAF	none	none
APAP	APAP	none	yes
SAL	SAL	yes	none

Neither CAF nor ASA (which has been converted to the monosodium salicylate) exhibit any absorbance from 255 to 340 mμ. Therefore, the SAL and APAP content of the tablets may be determined differentially at 330 mμ and 263.5 mμ, respectively, since

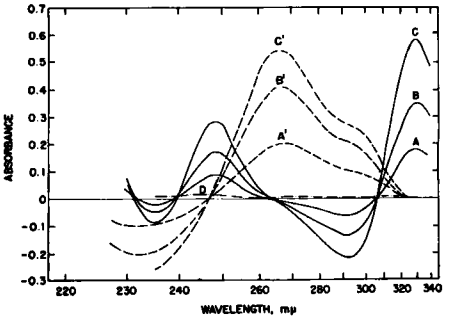


Fig. 5—Differential spectra of SAL (A, B, C), APAP (A', B', C'), and CAF + ASA (D).

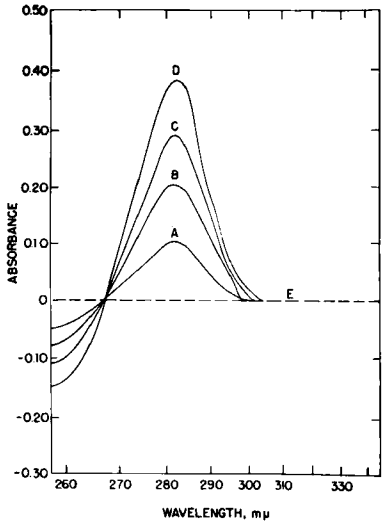


Fig. 6—Differential spectra of CAF (A, B, C, D) *and SAL + APAP + ASA* (E).

APAP shows no absorbance at 330 mμ, and SAL has an isosbestic point of zero absorbance at 263.5 mμ. A detailed explanation on the use of isosbestic point in spectrophotometry may be found (12). To ascertain that the pH 6 and pH 10 buffers cause maximum absorbance for APAP and SAL, pH 11 and pH 12 buffers were tried instead of the pH 10 buffer. As would be expected from the pK values of APAP and SAL, it was found that the pH 11 and pH 12 buffers caused an insignificant increase in absorbance over that of the pH 10 buffer.

In the differential spectrophotometric method for the determination of CAF, two buffer solutions are used—pH 1.3 and 1:10 HCl:H_2O solution. Since the pKa of the conjugated acid of caffeine is 0.61, caffeine exists predominantly as two different species at the two pH's.

Caffeine	Caffeine · H^+ (conjugated acid)
pH 1.3	1:10 HCl:H_2O

Therefore, caffeine should exhibit a differential spectrum between these pH's. Figure 6 demonstrates that CAF shows an absorbance maximum at 283 mμ. As expected from the pK values listed above, the other components exist as the unionized species in both buffers, and, therefore, exhibit no absorbance differentially. Unfortunately, the background effect is too great to permit absorbance readings to be taken in the optimum range of 0.42 absorbance units when the tablets are of standard composition. However, if tablets of different composition are analyzed (where the background absorbances are small), this procedure could prove to be very useful, since one could work at higher absorbances, with no interference from the other components.

In the caffeine extraction method, APAP, SAL, and ASA are converted to their sodium salts with sodium hydroxide and remain in the aqueous layer. The CAF, which is not affected by the sodium hydroxide can then be easily extracted from the other

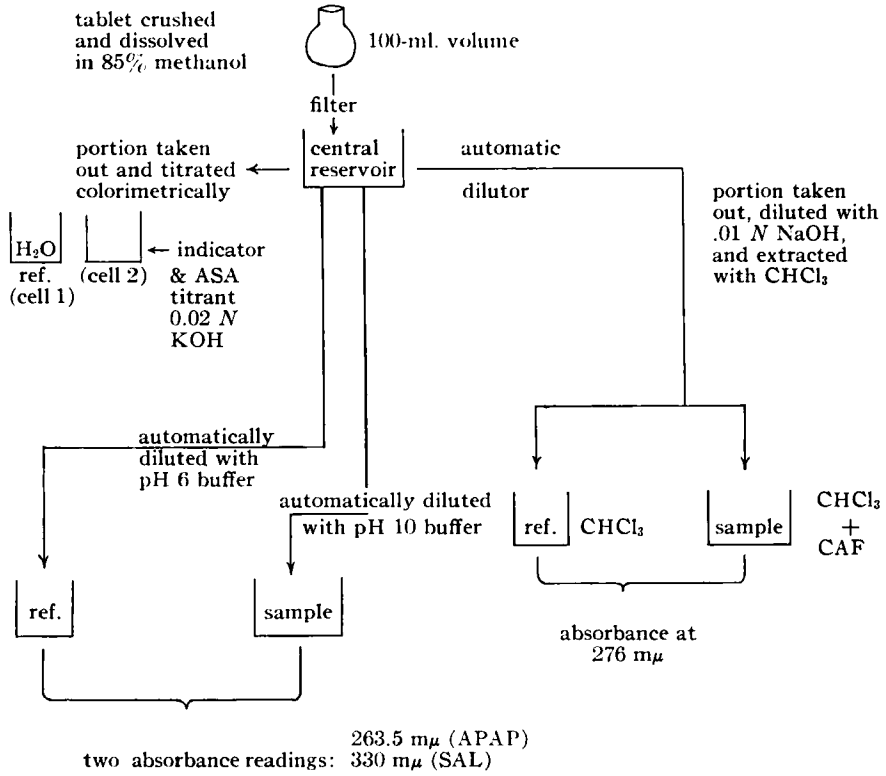


Fig. 7—Proposed schematic diagram for the automated system.

components with chloroform. However, it is imperative to use 0.01 *N* NaOH, because a stronger concentration of the base can change the CAF structure (17), and, therefore, cause erratic results.

Automation for the analysis of the four components can be performed by following the above procedures (extraction, rather than differential spectrophotometry is preferred for CAF). The results would be directly obtainable from the responses of the recorders without need of any computers or calculating devices. The proposed schematic diagram for the automated system is shown in Fig. 7.

The tablet is crushed and dissolved in 85% methanolic solution, which is filtered into a central reservoir. From this container, three portions are taken. One aliquot is colorimetrically titrated for ASA in the presence of dye indicator with 0.02 *N* KOH. A second aliquot is automatically diluted with a given quantity of 0.01 *N* sodium hydroxide, and the CAF is extracted into chloroform, which is read at 276 mμ *versus* chloroform on a spectrophotometer. A third portion is automatically diluted and separated into two segments. To one portion, a pH 6 buffer solution is added and passed through a reference flow cell located in a spectrophotometer. Simultaneously, a pH 10 buffer solution is added to the other segment of the solution and passed through a sample flow cell in the spectrophotometer. The wavelength scale is programmed rapidly to two wavelengths—263.5 and 330 mμ. The APAP and SAL are determined at 263.5 and 330 mμ, respectively.

The advantage of using these methods is that each specific procedure is independent of the concentrations of the other components, and therefore, can be used either in the presence of large quantities or in the absence of any of the other ingredients, with very good accuracy and precision.

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Keyphrases

Analgesic tablets, powders—analysis
Aspirin determination—analgesic mixture
Colorimetric titration—analysis
Salicylamide, acetaminophen determination—analgesic mixture
Caffeine determination—analgesic mixture
UV spectrophotometry—analysis

Application of Sugar Coating to Tablets and Confections by Means of an Automated Airless Spray System I

Investigation of the Direct Coating of Tablets

By G. M. KRAUSE and T. L. IORIO*

The practicability of directly applying sugar coating to unsubcoated tablets has been studied. Initial work performed indicates that such a procedure may be feasible when used in place of current sugar-coating techniques.

THE DEVELOPMENT of automated airless-spray film-coating methods has shown signs of significant growth in recent years (1–5). Although there is considerable information pertaining to film coating by this method, particularly with coating solutions consisting of organic solvents and polymeric materials, there is little if any descriptive literature pertaining to the use of aqueous solutions of sugar or syrups as the coating medium. At the present time, sugar

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