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Keyphrases

Tablets—sugar coating
Spray coating—automated airless system
Automated coating, pan coating—comparison

Semiautomated Assay for the Simultaneous Determination of Propoxyphene Hydrochloride and Paramethasone Acetate in Coated Single Tablets

By C. E. STEVENSON and I. COMER

A semiautomated method for the simultaneous determination of propoxyphene hydrochloride and paramethasone acetate is described for coated tablets. A novel device for the removal and dissolution of tablet coatings is outlined. Solutions are sampled with an automatic sampler at the rate of 20/hr. and fed to two independent systems for analysis. A modified blue tetrazolium procedure is utilized for the determination of paramethasone acetate producing essentially complete color development within 5 min. at room temperature. Working concentrations of 12.5 mcg. paramethasone acetate per ml. can be assayed without resorting to range expansion. Analysis of propoxyphene hydrochloride is accomplished by the formation of a complex with bromocresol purple with subsequent extraction and color measurement in ethylene dichloride.

THE AUTOMATED analysis of single tablets has been reported by Wolski (1) as a useful tool in the concept of quality assurance. The product[1] involved in this study consists of an enteric 500-mg. acetylsalicylic acid (aspirin) core tablet coated with 32.0 mg. of the analgesic propoxyphene hydrochloride (DPH), and 0.250 mg. of the ketosteroid paramethasone acetate (PMA) (6α-fluoro-16α-methylprednisolone 21-acetate). For the quality assurance of this product, an automated single-tablet procedure for the simultaneous determination of DPH and PMA was developed using the automatic analyzer.[2]

A desirable condition involving methods for simultaneous determinations is that each component be capable of measurement in the presence of the other without significant interference. The automated method of Kuzel (2), based on the formation of a complex between tertiary amines and bromocresol purple (BCP), and the automated methods of Greely *et al.* (3) and Beyer (4), utilizing the reducing powers of the ketosteroids on blue tetrazolium (BTZ), meet this condition for the compounds in this study. Slight modifications of these procedures have been made in the development of this automated system.

EXPERIMENTAL

Reagents—*BCP*—A 2% acetic acid–98% deionized water (v/v) solution containing 0.25 mg. of bromocresol purple (5′,5″-dibromo-*o*-cresolsulfonphthalein Na salt, Eastman No. 6266) per ml.; *BTZ*—A solution containing 0.15 mg. blue tetrazolium (Fisher Certified B-410) per ml. SD-3A alcohol; *Ethylene Dichloride*—Fisher Certified E-175; TMAH—A solution of 20% tetramethylammonium hydroxide (Eastman No. 1515)–80% SD-3A alcohol (v/v); *Wash*—A solution of 50% methanol–50% deionized water (v/v); *Theory Standard*—32.0 mg. propoxyphene hydrochloride and 0.250 mg. paramethasone acetate reference standard per 20 ml. of Wash solution.

Sample Preparation—Due to the relatively low steroid concentration in the formulation, it was desirable to limit the amount of solvent used in the dissolution of the active ingredients to as low a volume as possible. Utilization of an automatic[3] module

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[1] Marketed as Stero-Darvon with ASA by Eli Lilly and Co., Indianapolis, Ind.
[2] AutoAnalyzer, Technicon Corp., Chauncy, N. Y.
[3] Solidprep, Technicon Corp., Chauncy, N. Y.

was therefore undesirable. Since the single-tablet analysis of aspirin was not required, tablet coatings were removed using a stirring device designed by Coffy (5) and fitted with a Styrofoam block to hold twelve 25 × 100-mm. round-bottom centrifuge tubes. This apparatus is shown in Fig. 1. A 20-ml. aliquot of the Wash solution is added to each tube containing a 1.3-cm. Teflon-coated magnetic stirring bar and one tablet. The tube is then stoppered and placed in the stirring apparatus. After about 45 min. of mixing, complete removal of the tablet coatings and dissolution of the active ingredients is achieved. The tablet core and the stirring bar are then removed and the solution centrifuged to settle the undissolved particles. Two 8.5-ml. sample cups are filled with the supernatant liquid for duplicate analysis in the automatic analyzer system.

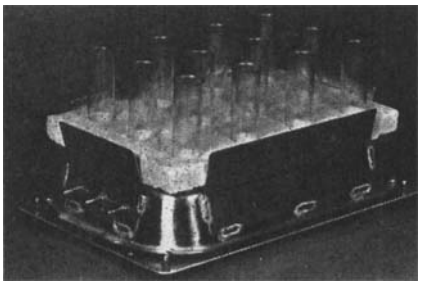

Fig. 1—Tablet dissolution apparatus.

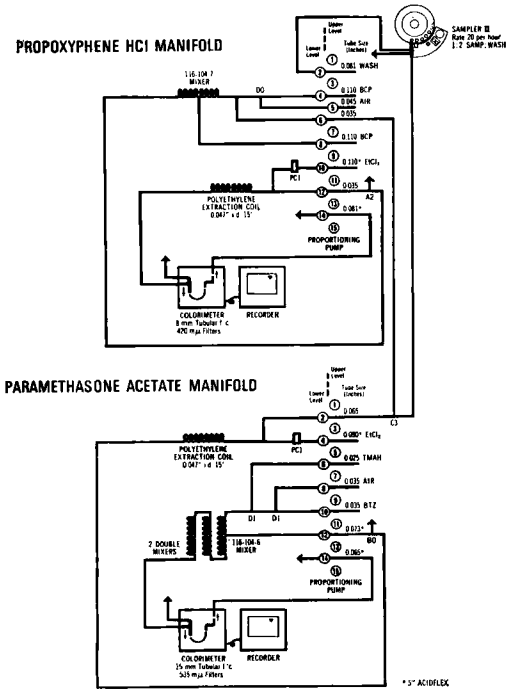

Fig. 2—Flow diagram.

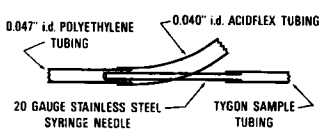

Fig. 3—Special fitting.

Procedure—The complete analytical system is outlined in the flow diagram shown in Fig. 2. The sample solution is aspirated from the liquid Sampler II and flows directly to the C3 debubbler where an unsegmented sample is taken for the PMA manifold. The remaining sample, still isolated between the air bubbles produced during sampling, flows to the DPH manifold where it is injected into an air segmented stream of BCP. This stream is further diluted with BCP and an unsegmented resample is taken at the A2 fitting. This sample is then segmented into a stream of ethylene dichloride ($EtCl_2$) by means of a fitting, previously described by Kuzel (2), and shown in Fig. 3. Extraction of the dye complex is carried out in the polyethylene mixing coil, with subsequent color measurement of the $EtCl_2$ extract after separation from the aqueous stream.

The sample taken at the PMA manifold is immediately segmented into a stream of $EtCl_2$, again using the fitting diagrammed in Fig. 3. Extraction of the PMA into the $EtCl_2$ occurs, and the unsegmented $EtCl_2$ extract is resampled from the bottom of the BO fitting. This sample is injected into an air segmented stream of BTZ and TMAH, mixed through the equivalent of five small mixing coils, and the stream debubbled before measurement in the colorimeter.

Glass wool plugs are inserted in the exit ports of both PCl pulse chambers and in the middle entrance port of the mixing coil 116-104-6 in the PMA manifold. This is done to prevent any flakes of Acidflex tubing from entering the analytical train.

In practice, five theory standards are sampled initially and the standard deviation calculated. Ten samples are then assayed in duplicate followed by standards in duplicate throughout the entire run. If the duplicate standards fall outside the range of 2 σ calculated from the first five standards, the duplicate standards are considered the appropriate values for use in the calculation of the results for the following group of samples. Normally, very little drift is experienced.

RESULTS AND DISCUSSION

The various parameters of the simultaneous methods were investigated. All concentration values listed in the figures are per 20 ml. of the Wash solution and all data were collected from combination standards of DPH and PMA unless otherwise indicated. With the exception of the BCP reagent, the brands of reagents used in this procedure were arbitrarily chosen.

Linearity of the DPH response is shown in Fig. 4 by the straight line connecting the appropriate peaks in the standard curve. All DPH data were collected on a Technicon linearized recorder. The standard curve of PMA is shown in Fig. 5. Since a normal output recorder was used in the collection of the PMA data, the pen response was charted on logarithmic paper. A plot of the absorbance values (Fig. 5) *versus* PMA concentrations results in a straight line passing through the origin. The 60-sec. sampling of the solutions in the procedure produces peak heights which are 77% of the steady state (continuous sampling response) for the PMA system and

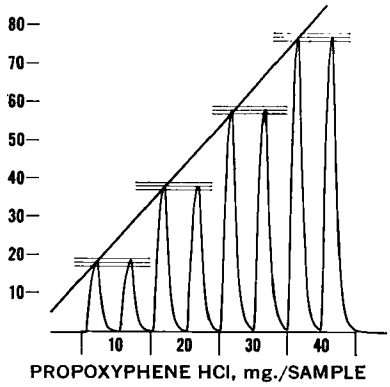

Fig. 4—Propoxyphene HCl standard curve.

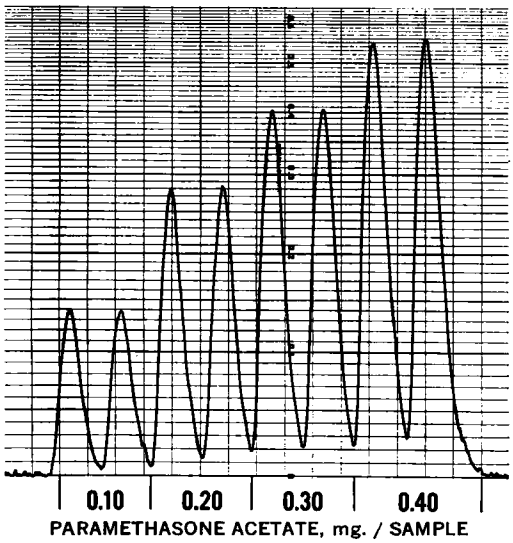

Fig. 5—Parametasone acetetate standard curve.

87% of steady state for the DPH system. Ten repetitive samplings of the Theory Standard solution demonstrated the excellent repeatability of the systems. A relative standard deviation (*RSD*) of only 0.81% was obtained from the DPH system while the PMA system produced a *RSD* of 1.11%. The effect of varying concentrations of PMA on DPH standards and of DPH on PMA standards was studied. No significant interference was observed in either system.

A placebo tablet was assayed by this procedure using 20 ml. of the Theory Standard solution to remove the tablet coating. The supernatant liquid was assayed along with the pure standard solution. An interference of minus 2% for the DPH determination and plus 2% for the PMA determination was observed.

Due to the possibility of a breakthrough of aspirin from the tablet core during coating dissolution, the effect of aspirin upon the response of DPH and PMA standards was studied. No change in DPH response to varying concentrations of aspirin was observed; however, as indicated in Fig. 6, aspirin levels somewhere between 100 mg. and 250 mg. begin to cause a decrease in the PMA response. At the level of 500

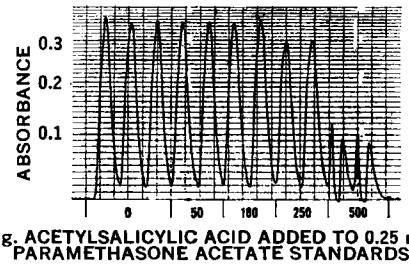

Fig. 6—Effect of acetylsalicylic acid on parametasone response.

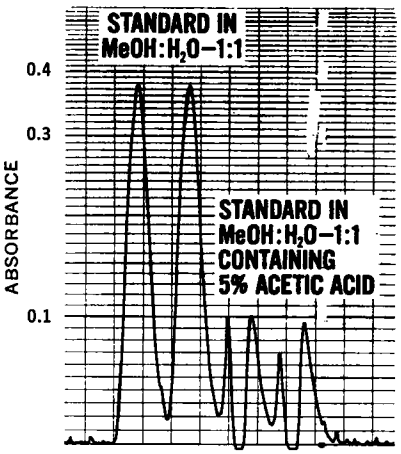

Fig. 7—Effect of acetic acid on parametasone acetate response.

mg., a peak inversion is observed. Since a basic solution is required for the BTZ reduction, it was postulated that the aspirin was producing an acidic condition which inhibited the color development. Addition of acetic acid to the standard solution as shown in Fig. 7, gave the same characteristic peak inversion obtained from the 500-mg. aspirin sample in Fig. 6.

Ten samples were taken at random from an experimental lot of tablets and assayed by the automated procedure. An average of 32.4 mg. DPH and 0.260 mg. PMA per tablet was found with a *RSD* of 5.6 and 6.5%, respectively, including tablet heterogeneity. Results obtained from this lot of tablets by a manual procedure based on a composite sample of 10 tablets were 32.3 mg. DPH and 0.253 mg. PMA per tablet.

As a result of the low PMA concentration in the formulation, the PMA manifold was designed to resample as large an amount of the $EtCl_2$ extract as possible. This in turn was injected into a minimum volume of the BTZ–TMAH reagent. Surprisingly, this resulted in a very rapid color development in the automatic analyzer system. The equivalent of only five small mixing coils was used to develop the color at room temperature. The addition of several more mixing coils before the colorimeter resulted in a relatively small increase in color intensity. Previously automated methods specify either a double holding coil (3) or a 37° heating bath (4) at this point in the flow system. In order to obtain an explanation for this accelerated color development, a study was carried out varying the percentage of

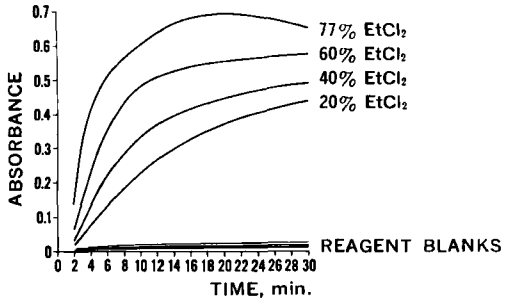

Fig. 8—BTZ–paramethasone acetate color formation.

$EtCl_2$ in the reaction mixture. The reagents used in this study were prepared as follows: 5 ml. of TMAH (10% aqueous solution) was diluted to 100 ml. with SD-3A alcohol; 25 mg. of BTZ was dissolved in 5 ml. of methanol and then diluted to 100 ml. with $EtCl_2$; 30 mg. of PMA was dissolved in 200 ml. $EtCl_2$.

Two milliliters of the PMA solution was added to four 25-ml. volumetric flasks, followed by 3 ml. of the BTZ solution; 0, 5, 10, and 15 ml. of SD-3A alcohol were pipeted into the flasks, followed by $EtCl_2$ to give a volume of about 19 ml. Five milliliters of the TMAH reagent was then added (time zero) and the solution diluted to the mark with $EtCl_2$. Reagent blanks were run substituting $EtCl_2$ for the PMA solution. The absorbance measurements used to plot Fig. 8 were obtained on a Perkin-Elmer Hitachi 139 spectrophotometer. These data show a marked acceleration of color development with increasing concentrations of $EtCl_2$. The same accelerated reaction is obtained by substituting chloroform for $EtCl_2$. Other keto-steroids (cortisone acetate, hydrocortisone acetate, prednisone, prednisolone, and flurandrenolone) assayed in both 20% and 60% $EtCl_2$, gave similar accelerated color development in the solution of greater $EtCl_2$ concentration.

Because the $EtCl_2$ concentration in the automatic analyzer system is approximately 70% and the color measured after only a 5-min. reaction time, it would seem likely from Fig. 8 that the addition of mixing coils to increase the reaction time would substantially increase the color intensity. Since this is not the case, it is speculated that the constant mixing in the automatic analyzer coils may accelerate the reaction even more than that observed by the static manual technique.

SUMMARY

An automated method for the simultaneous determination of DPH and PMA has been described. A technique for the removal of tablet coatings which may be of value in formulations of a similar nature is outlined. A further description of the construction of the stirring apparatus used in this technique was given by Comer *et al.* (6). Various parameters of the simultaneous analysis have been discussed. Due to the functional group specificity of the methods, it is probable they could be used for the simultaneous analysis of most combinations of keto-steroids and tertiary amines. It has also been demonstrated that by carrying out the steroid BTZ reduction in high concentration $EtCl_2$ solutions, an accelerated color development occurs. This knowledge, applied to the existing USP (7) and NF (8) steroid methods, could reduce the time required for these manual determinations.

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Keyphrases

Automated analysis—single tablet
Propoxyphene HCl—paramethasone acetate on aspirin core
Bromocresol purple reagent—propoxyphene HCl
Paramethasone acetate—blue tetrazolium reagent
Diagram—automated apparatus
Colorimetric analysis