Automated IR Technique for Determination of Methylphenidate Hydrochloride in Tablet Formulation

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Abstract □ A new automated method has been developed for the determination of methylphenidate hydrochloride in pharmaceutical formulations using IR absorption. The weakly reactive ester possesses an isolated absorption band in the IR region. The method is specific for the ester carbonyl band and it is more reliable than any other method found in the literature. Since the determination is based on an extraction of the intact ester into a chloroform solution, the proposed method shows stability and will strengthen the application as an analytical method in the pharmaceutical industry.

Keyphrases □ Methylphenidate HCl tablets—automated analysis □ Automated procedure—methylphenidate HCl determination in tablets □ Stability-indicating procedure—methylphenidate HCl tablets □ IR spectrophotometry—automated analysis procedure

Spectrophotometric methods such as UV, visible, or fluorometric techniques are commonly available for the determination of active ingredients in unit dosage pharmaceutical preparations. The unique sensitivity of these methods in unquestionable. However, with the gain in sensitivity, there is a corresponding loss in specificity. The IR absorption has a unique specificity as a photometric method, but until now it has been neglected because of its lack of sensitivity for the quantitative determination of pharmaceutical preparations. Its application is becoming more significant with the introduction of commercially available high-resolution instruments.

The usefulness of IR absorption as an advantageous quantitative technique for the determination of an ester in pharmaceutical preparations is generally recognized. Preparations containing ester groups undergo chemical reactions fairly easily and may cause pharmacological deactivation of the active drug. Methods suitable for the determination of the decomposition product as well as for the content uniformity per unit dosage, with good precision, were needed. The IR technique was successfully used for the determination of the intact ester in one tablet formulation when the other methods failed to work.

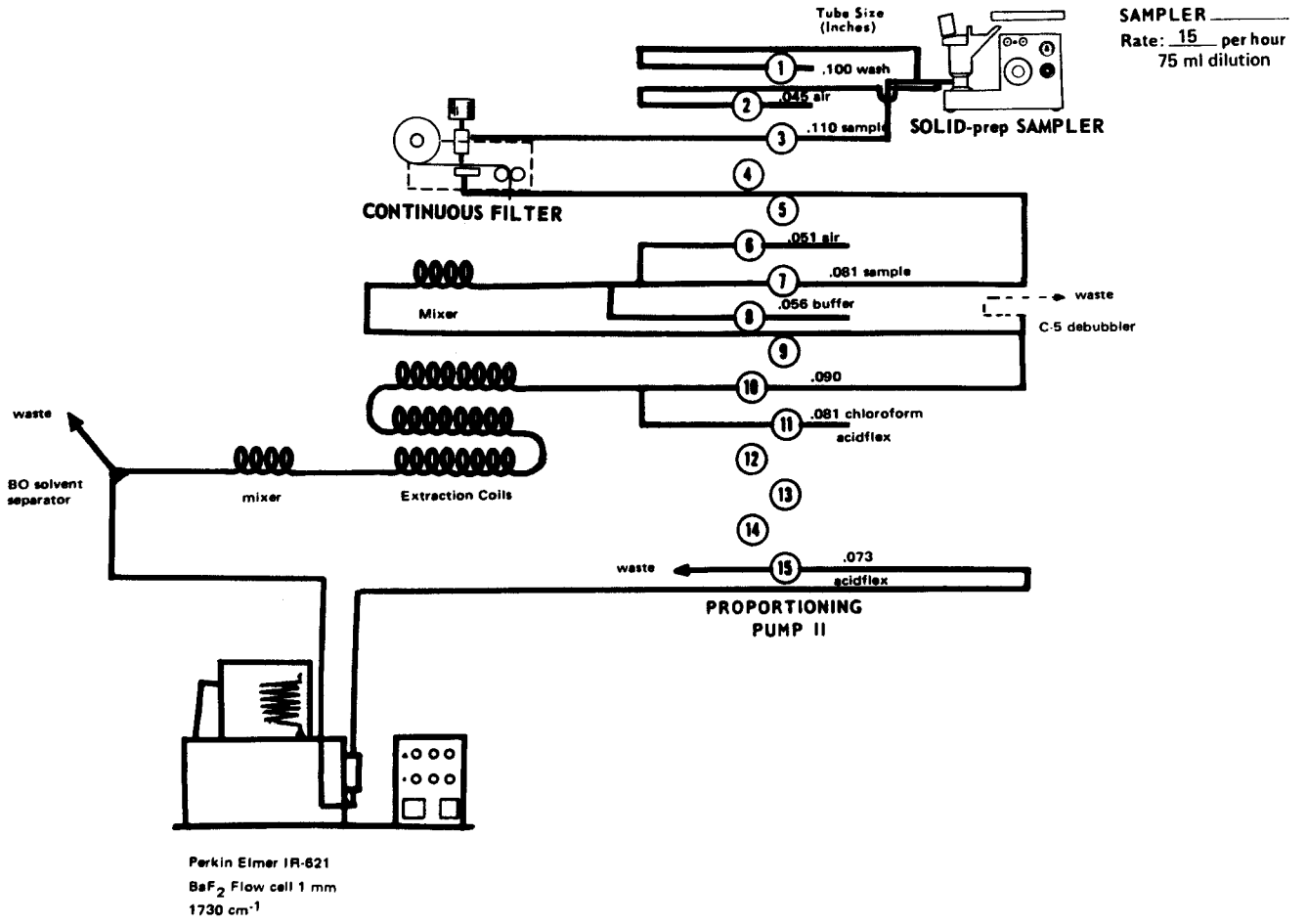

Figure 1—*Schematic diagram indicating the keys of the flow diagram, the automated equipment used for the analytical procedure, and the special tubing where necessary.*

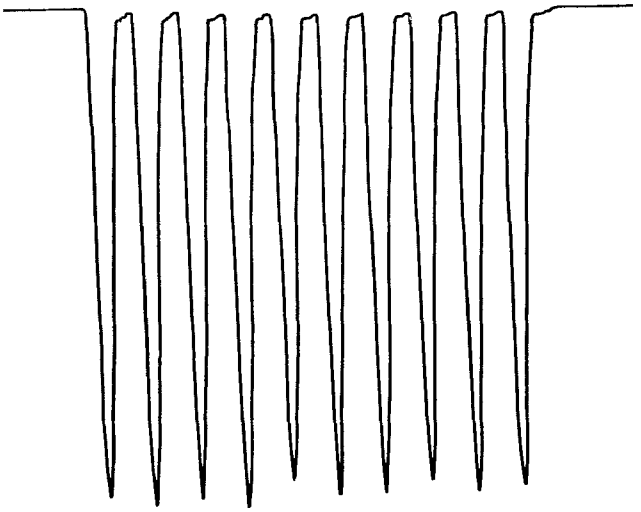

Figure 2—*Typical recording of consecutive standards.*

Several manual methods have been reported for the determination of compounds containing an ester as a functional group. Compounds that do not contain aromatic amino or hydroxy groups can be directly detected with 4-aminophenazone after complete saponification (1). This method is specific for 4-hydroxybenzoic acid rather than an ester. The specificity of the chromatographic determination of esters was also reported (2). The esters were separated on thick silica gel layers and determined colorimetrically using different reagents. This manual method is not suitable for automation because of technical difficulties.

IR spectra are often used for the identification of esters in the region of 1050–1350 cm.$^{-1}$ (3). This region is characteristic of the acyloxy moiety. Saturated aliphatic esters have characteristic absorption in the far IR region (350–50 cm.$^{-1}$) (4). The band frequency correlations are classified by the alcohol components for which these spectra provide particularly useful identifications. Although these bands are useful for qualitative identification, the band intensities are not strong enough for quantitative determination.

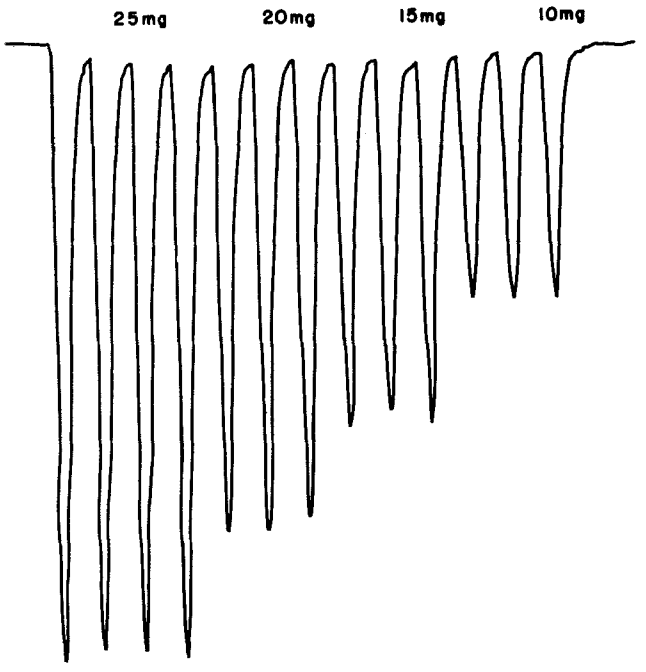

Figure 3—*Beer–Lambert curves for absorbance* versus *concentration.*

Table I—Repeatability of Standard Values by Automated Analysis

Number	Absorbance[a]
1	0.0226
2	0.0230
3	0.0229
4	0.0233
5	0.0221
6	0.0229
7	0.0228
8	0.0221
9	0.0228
10	0.0225

[a] Absorbance: low = 0.0221, average = 0.0227, high = 0.0233, and SD = 1.65%.

A very specific qualitative colorimetric test consists of converting the ester to hydroxamic acid, which forms a color complex with ferric ion (5). This qualitative test was lately converted into a quantitative method (6), but the color development is pH dependent and the precision is dependent on reagent purity.

Among the large number of substances subjected to automated analysis, the esters are perhaps the analytes that need more meaningful consideration in the technology for their determination. The IR technique undoubtedly will strengthen the overall analysis in the pharmaceutical field; perhaps it will soon become a more popular, common, analytical technique in automated analysis.

EXPERIMENTAL

Apparatus—A standard Technicon automatic AutoAnalyzer system consisting of the following modules was used: SOLIDprep sampler II, programmed at 15 samples/hr.; proportioning pump II; continuous filter, speed at 3.5; and Perkin-Elmer IR 621 equipped with 1-mm. Beckman barium fluoride liquid cells, steady wavelength at 1730 cm.$^{-1}$, with a chart speed of 10 min./in. and with 10× ordinate scale expansion.

Reagents and Solutions—*Solvents*—The following were used: chloroform, reagent grade; distilled water; and bicarbonate buffer (dissolve 25.2 g. sodium bicarbonate and 31.8 g. of sodium carbonate in 1000 ml. of distilled water).

Standard Preparation—Dissolve 426.4 mg. of methylphenidate hydrochloride in 100 ml. of distilled water.

Automated Procedure—The schematic diagram of Fig. 1 indicates the keys of the flow diagram, the automated equipment used for the analytical procedure, and the special tubing where necessary. In performing the complete automated analysis, tablets were placed individually into the SOLIDprep sampler turntable cups and the system was activated. The tablets were ground to a fine powder in the blender and dissolved in 75 ml. of water for a period of 1.75 min. (45% of the complete 4-min. cycle); the sampling time was 30% and the rinsing time 25% of the complete cycle. A continuous filter was adapted to filter off the undesirable, insoluble tablet excipients from the solution before mixing with solvents. The clear filtrate was segmented with air and combined with a stream of buffer solution. The sample stream and buffer passed through a single mixing coil to obtain complete mixing. Then the debubbled solution was pumped through three horizontal double-extraction coils to permit sufficient extraction. The chloroform–buffer mixture was passed again through a mixing coil before reaching the solvent separator. The chloroform solution then was sucked through the liquid cell for spectral measurement against the chloroform in the reference cell.

Five-milliliter aliquots of standards were introduced at the proper intervals during the measurements, and the absorption of the carbonyl band of the tablets' active ingredient and standards were re-

Table II—Comparison of Results Obtained by Automated and Official Methods for Methylphenidate Tablets

Automated Method[a]						Official Method[b]	
Number	Absorbance	Milligrams/ Tablet	Number	Absorbance	Milligrams/ Tablet	Number	Milligrams/ Tablet
1	0.0213	19.7	11	0.0209	19.4	1	20.5
2	0.0209	19.4	12	0.0215	19.9	2	19.7
3	0.0204	18.9	13	0.0215	19.9	4	20.2
4	0.0218	20.2	14	0.0204	18.9	4	19.6
5	0.0210	19.4	15	0.0205	18.9	5	19.7
6	0.0219	20.3	16	0.0204	18.9	6	20.2
7	0.0214	19.8	17	0.0215	19.9	7	20.0
8	0.0220	20.4	18	0.0205	18.9	8	20.7
9	0.0210	19.4	19	0.0202	18.7	9	20.5
10	0.0224	20.7	20	0.0222	20.6	10	20.6

[a] Low = 18.7 mg./tablet, average = 19.6 mg./tablet, high = 20.7 mg./tablet, and SD = 3.2%. [b] Low = 19.6 mg./tablet, average = 20.2 mg./tablet, high = 20.7 mg./tablet, and SD = 1.4%.

corded on the IR instrument recorder. Using the common baseline technique, the content per dosage form was calculated.

DISCUSSION

Automation as a routine chemical analysis has been used for 20 years in the field of analytical chemistry. Although automation has been used mostly for clinical testing, the technique has reached widespread application in industry, especially in pharmaceutical chemical analysis. Since content uniformity testing has become official in the USP and NF, automation achieved popularity as one of the most efficient and economical methods of analysis in process control. Because of the great demand in clinical and biological testing, the automated instruments available on the market were prepared especially for the handling of liquids rather than for solids for these laboratories. Difficulties were encountered in automating pharmaceutical preparations, namely in the disintegration and dissolution of tablets in suitable solvents using the SOLIDprep unit[1].

This paper describes a fully automated method; the sampling and dissolution processes do not require manual operations. Until now, very few such methods were proposed in the literature. Fortunately, in this study no difficulties were encountered in disintegration or dissolution of methylphenidate tablets, and the best synergism of disintegration and dissolution was found in distilled water.

In the initial phase of preparing the manifold, experiments were performed to determine the optimum buffer composition to obtain the most effective extraction of the active ingredient through the extraction coils. Various buffer solutions, such as borate, citrate, and phosphate with well-defined pH values of 9.5–10.0, were tested. While these buffer solutions followed the Beer–Lambert law for manual measurement, a continuous background change was observed. The cause of this change is unknown. It may be due to decomposition or from interaction between the methylphenidate and buffer solution. More realistic and reproducible extraction with a steady background was obtained when carbonate buffer solution was used to convert the acid salt to an undecomposed, chloroform-soluble free ester. Although the stability of the methylphenidate in this buffer solution is affected by time, significant decomposition was found only after 5–10 min. of standing in buffer solution. Since the time that elapsed in contact of sample solution with the buffer prior to extraction was less than 1 min., the possible decomposition of the sample solution was eliminated.

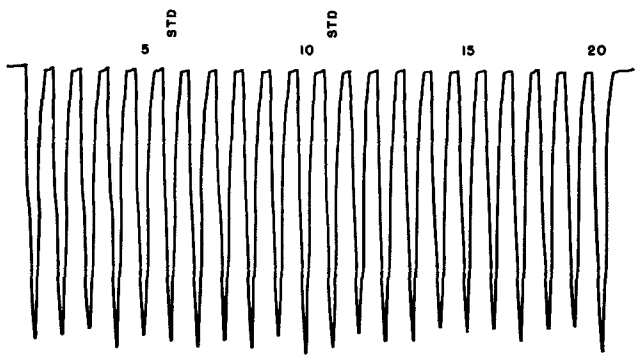

Figure 4—*Curves of regular production tablets.*

[1] Technicon Corp.

In the second phase of this study, the effectiveness of the chloroform extraction was investigated. Mechanical shaking of the sample solution with chloroform gave satisfactory extraction; however, technical difficulties appeared in the performance. Passing the chloroform–buffer solution through an ultrasonic bath resulted in a cloudy solution without clear separation. Using the Technicon extraction coil, a clear solution was obtained; however, the efficiency of one coil was inadequate. Three extraction coils in series gave about 80% recovery of the active ingredient, which was sufficient for spectrometric measurement.

To obtain reliable absorbance values, the instrument was set on 10× expansion scale and deviation of ±0.0006 absorbance was recorded on 10 replicate standard solutions. Figure 2 shows the consecutive standard curves using the IR absorption technique. Evaluating the recorded curves, one can see a stable baseline with fairly good reproducibility and clean backwash. The variation of the standard concentrations is demonstrated in Fig. 3. The plotted curve, prepared from the average peak readings *versus* its concentration, resulted in a straight line which passed through the origin. Table I summarizes the individual absorbance values on the standards with the standard deviation. After reliable indications on standards were obtained, regular production tablets containing 20 mg./tablet were subjected to complete automated testing. The results of this test can be seen in Fig. 4. Table II incorporates the comparative results obtained by official and automated techniques. From this table, it is evident that the automated method is reliable and useful for the determination of unit dosage in individual tablets. Although the results in Table II were obtained on 20-mg. tablets, the proposed method is applicable for 10-mg. tablets and, with a slight modification of the instrument, for 5-mg. tablets as well.

The instrumental system for this study was extremely stable; however, the acidflex tubes conducting the chloroform solutions lose their elasticity after a certain time, which may cause a significant change in the assay. This problem can be minimized by replacing the acidflex tubing periodically.

CONCLUSION

The goal of this study was to develop a quantitative method suitable for content uniformity testing that can be automated and is stability indicating.

The IR method was successfully applied for the determination of the intact ester carbonyl after a simple extraction procedure. The extraction was necessary to separate the ester from interfering materials that have absorption in the same region. The commonly used methods, *i.e.*, colorimetric and titrimetic, cannot be applied because of interferences.

This paper presents a preliminary work on a new technique for detection in automated analysis. The dependence of buffer solutions upon the nature of extraction and the intensity of measurable band with the other parameters is discussed. As a new application in automation, the advantages of the technique are demonstrated.

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Impact Test for Hardness of Compressed Powder Compacts

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Abstract □ An impact–rebound method of estimating the hardness (*i.e.*, the pressure necessary to produce permanent deformation) of a compact of powdered solid is evaluated. A steel sphere arranged as a pendulum acts as the indenter. Since energy consumed during impact is used in doing pressure–volume work, this energy divided by the volume of the indentation provides an estimate of the mean deformation pressure. Two methods of estimating the dent volumes are compared. The simpler method uses equations adopted from metallurgy. These estimate the volume from the energy consumed during impact and the chordal radius of the dent. The alternate method estimates the volume from the displacement of a grid of lines projected onto the dented surface at a small angle of incidence. The latter method gives slightly smaller volumes than the former. When plotted in various ways, the data obtained yield slopes and/or intercepts consistent with the adopted metallurgical equations. Therefore, these equations are considered to provide: (*a*) an acceptable description of the indentation process and (*b*) the more satisfactory method of estimating the hardness of compacts. Plots of log pressure *versus* relative density appear to be linear. Extrapolations of these plots to a relative density of unity provide estimates of the properties of a single polycrystalline mass of the powdered material.

Keyphrases □ Powder compacts, compressed—impact test □ Compressed powder compacts—impact–rebound hardness test □ Indentation volume measurement—compressed powder compacts □ Diagram—pendulum impact device

In previous communications (1–3), the senior author indicated that the mechanical properties of solids are important fundamental properties which affect the flow and bonding properties of solids. Shlanta and Milosovich (4) studied some of the time-dependent effects, and Shlanta (5) reviewed the importance of plastic deformation in tableting. Huffine (6) also considered these properties. Because the anelastic properties of crystalline solids are dependent not only on the strength of the intermolecular interactions but also on the degree of imperfection of the molecular arrangement, the plastic yield pressure is not an intrinsic property of the solid state of a chemical compound in a given polymorphic form. The procedure followed in crystallizing the compound and the subsequent working of the solid may influence the plastic yield value.

Hardness may be defined as the resistance of a solid to permanent deformation (7). Indentation methods are standardized and are common practice for assessing the hardness of metals. Previous reports in the pharmaceutical literature (8–10) of the use of indentation methods have not established whether the equations used with metals may be applied to compacts of organic materials. It is the purpose of this article to explore this aspect for the dynamic, *i.e.*, the impact–rebound, method of hardness testing. The theoretical equations adopted from the metallurgical field are described later in this communication.

APPARATUS

The pendulum arrangement for controlling the pathway of a sphere is used in this apparatus. This arrangement simplifies the control and measurement of the initial and rebound height. Figure 1 shows the apparatus diagrammatically. Figure 2 is a photograph of the apparatus (an air shield was removed to expose the apparatus).

Two dies are used in these studies: one is of square cross section and the other is circular. Both have a cross-sectional area of 2.25 in.^{2}. Eight to twenty grams of powdered solid is used in the die. The compact is pressed with a hydraulic press[1]. The die is held between the punches only by the friction with the powder, thereby permitting both punches to move. To increase the probability of a series of tablets having identical properties, the pressure is raised to a selected value and maintained for a definite time. Figure 3 shows the two dies with one punch and the compact in place.

EXPERIMENTAL PROCEDURE

After removal from the press, the compact is pushed to within a couple of millimeters of the surface of the die. The die, F, containing the compact, B, and longer punch, G, are clamped into the apparatus by means of clamps, J. The back-up block, H, is moved up to the punch and its bolts are tightened only moderately. Bolt I is then used to push against the support post, N, until enough force is developed to push the back-up block, the punch, and the compact until the compact is moved flush with the die surface. The bolts on the back-up block are then tightened. Thus, only one face of the solid is left unsupported.

The sphere, A, is raised against the pointed pole of the magnetic hold, E. Both a.c. and d.c. currents are used initially to cause the sphere to vibrate against E and seek an equilibrium orientation. Before release, the a.c. signal is removed and the sphere comes to rest held by the d.c. field only. The sphere is released by opening the d.c.

[1] Model 341-20, Loomis Engineering and Manufacturing Co., Caldwell, N. J.