Quantitative Analysis of the Active Tablet Ingredient by Powder X-Ray Diffractometry

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A powder X-ray diffraction technique has been developed for the quantitative analysis of the active ingredient in intact tablets. Two model drugs were used: lithium carbonate (LC) and carbamazepine (CBZ). Mixtures containing various weight fractions of each drug and microcrystalline cellulose were compressed into tablets and the integrated intensities of several diffraction lines of each were used for quantitative purposes. The ratio of the integrated intensity of these lines in tablets, made from mixtures of drug and microcrystalline cellulose, to the intensity of the same lines in tablets made from only drug was calculated as a function of the weight fraction of the drug in the mixture. These ratios were also experimentally determined and the relative error in the determination of LC was less than 12%. CBZ tablets containing starch were also prepared. In the CBZ tablets containing microcrystalline cellulose or starch, the relative error in the determination of CBZ was less than 10% only when the weight fraction of CBZ in the tablets was ≥ 0.4.

KEY WORDS: quantitative powder X-ray diffractometry; tablets; carbamazepine; lithium carbonate.

INTRODUCTION

Tablet dosage forms have to fulfill several requirements before they are considered acceptable by the United States Pharmacopeia (1). In order to ensure that the amount of the active ingredient in the tablets is within acceptable limits of the labeled amount, the Pharmacopeia requires that the finished dosage form be assayed. Chromatographic methods are widely used to assay the active ingredient in tablets.

Quantitative analysis of mixtures of solids by powder X-ray diffractometry is possible. The theoretical basis of this technique was developed by Alexander and Klug (2,3). There are numerous examples in the literature of analysis of inorganic and organic mixtures by quantitative powder X-ray diffractometry (3,4).

Recently we determined the relative amounts of anhydrous carbamazepine, $C_{15}H_{12}N_2O$, and carbamazepine dihydrate, $C_{15}H_{12}N_2O \cdot 2H_2O$, in a mixture by quantitative powder X-ray diffractometry (5). Mixtures containing various weight fractions of the two were compressed into tablets prior to analysis. This was necessary because the powder samples yielded unsatisfactory results. When compressed to a certain pressure, the particles tended to orient the same way in replicate samples resulting in highly reproducible intensity values. The object of this investigation was to develop a powder X-ray diffraction technique to quantify the active ingredient in tablet formulations. This system has the following advantages: (i) the intact tablet can be mounted in a holder and analyzed directly; and (ii) in most solids, the exposure to X-ray for short periods of time is unlikely to cause sample decomposition. Therefore, the technique is nondestructive.

Lithium carbonate (LC) and carbamazepine (CBZ) were chosen as model drugs. Because of the preliminary nature of the study, only very simple systems were studied. Tablets were prepared by mixing the active ingredient with only one excipient. Mixtures containing various weight fractions of each drug and the excipient were compressed into tablets and their powder X-ray diffraction patterns were obtained.

MATERIALS AND METHODS

Materials. Lithium carbonate (LC) [Analytical Reagent; assay (Li_2CO_3), 99.61%] was supplied by Mallinckrodt (Paris, KY). Anhydrous carbamazepine (CBZ) [assay ($C_{15}H_{12}N_2O$), >99%] was obtained from Sigma Chemical Company (St. Louis, MO). It was ground in a ball mill (Spex Mixer/Mill, Spex Industries, Metuchen, NJ) for 5 min using a sample holder and ball made of agate. Microcrystalline cellulose (Avicel PH-105) and corn starch (Pure-Dent B810) were gifts from the FMC Corporation (Philadelphia, PA) and the Grain Processing Corporation (Muscatine, IA), respectively. Ceric oxide was a Standard Reference Material supplied by the National Institute of Standards and Technology (Gaithersburg, MD). All the compounds were stored under ambient conditions (≈25°C) in tightly capped bottles.

Weight Loss on Drying. The weight loss on drying of starch and microcrystalline cellulose was determined according to the procedure outlined in the USP (1). The starch was heated at 120°C for 4 hr. Microcrystalline cellulose was heated at 105°C to constant weight.

Thermal Analysis. The system consisted of a thermogravimetric analyzer (Du Pont 951) attached to a data analysis system (Thermal Analyst 2000, Du Pont). About 10 mg of the sample was weighed into an aluminum sample pan and heated under a stream of nitrogen. LC and CBZ were heated from 30 to 175°C, while the microcrystalline cellulose and starch were heated from 30 to 120°C.

Powder X-Ray Diffractometry. The tablets were exposed to CuKα radiation (40 kV × 30 mA) in the step-scan mode with increments of 0.02° 2θ in a Siemens (Model D500) wide-angle X-ray diffractometer. The Bragg-Brentano focusing geometry was used, with a 1° incident aperture slit, a 0.15° detector slit, and a scintillation counter as the detector. Counts were accumulated for 1 sec at each step.

Preparation of Lithium Carbonate Tablets. Mixtures containing different weight fractions of LC and microcrystalline cellulose were prepared. Three hundred milligrams of the sample was accurately weighed and compressed in a hydraulic press (Fred S. Carver, Menomonee Falls, WI) to a pressure of 136 MPa and held for 5 min. The tablets obtained were 11.2 mm in diameter and about 2.2 mm thick. A glass X-ray sample holder, with a central cavity 11.5 mm in diameter, was fabricated. The cavity had a depth of approximately 2.5 mm. Two small pieces of molding clay were put at the bottom of the holder, the tablet was dropped into the

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cavity, and using a flat glass slide, the tablet was gently pressed down until the holder surface and the tablet surface were coplanar. The use of a glass holder was necessary because aluminum diffracts X-rays between 35 and 40° 2θ. The tablets were scanned from 20 to 42° 2θ. Eight lines of LC were used for the quantitative purposes and Table I contains the Miller indices of these lines. The angular range over which integration was carried out to obtain the area under these lines is also given in the table. Once the powder diffraction pattern was obtained, the software in the instrument permitted automatic subtraction of the background (6). This eliminated the need for manual subtraction of the background counts for each peak. In an earlier study, the manual background subtraction was successfully used in quantitative X-ray analysis (5). However, such a correction would have been tedious in this study for two reasons. (i) We were interested in the integrated intensity of numerous lines. So the background correction would have had to be performed for each line. (ii) The powder X-ray diffraction patterns of the samples revealed that it would have been inappropriate to assume that the background counts do not undergo any change as a function of the scanning angle. Therefore the background counts would have had to be determined in the region immediately surrounding each line.

Table I. The Lines of Lithium Carbonate and Carbamazepine Used in the Quantitative Analysis (7,9)

d-spacings, Å	Miller indices	Integration angles, degrees 2Θ
	Lithium carbonate	
3.03	111	28.84–29.80
2.92	−202	29.92–31.00
2.81	002	31.06–32.62
2.63	−112	33.42–34.48
2.49	020	35.62–36.28
2.43	−311	36.38–37.30
2.28 2.26	021 310	38.96–40.12[a]
	Carbamazepine	
6.94 6.77	200 −101	12.36–13.28[a]
6.49	101	13.32–13.82
6.24	011	13.82–14.38
5.90 5.79	210 −111	14.38–15.52[a]
5.60 5.58	111 020	15.52–16.12[a]
5.18	120	16.52–17.50[b]
4.74	−211	18.02–18.96[b]
4.55 4.49	211 021	18.96–19.92[a,b]
4.35 4.30	220 −121	19.92–21.06[a,b]
4.04	−301	21.30–22.42[b]
3.80	−311	22.42–23.60[b]
3.72	221	23.60–24.20[b]
3.59 3.57	130 012, 320	24.20–25.66[a]
3.38 3.34 3.28	−202 031 230	25.70–28.26[a]
2.81 2.79	222 040, −421	31.20–32.42[a]

[a] Because of overlap, these lines were integrated as one peak.
[b] These lines could not be used in the analyses of tablets containing carbamazepine and microcrystalline cellulose.

Preparation of Carbamazepine Tablets. Since a major fraction of pharmaceuticals are organic compounds, this system was studied in greater detail than the inorganic system. Tablets containing CBZ and microcrystalline cellulose as well as tablets containing CBZ and starch were prepared. Two hundred milligrams of the sample was accurately weighed and compressed in a hydraulic press to a pressure of 90 MPa and held for 1 min. The tablets were 11.2 mm in diameter and 2 mm thick. An aluminum sample holder with a circular central cavity, 11.3 mm in diameter and 2.3 mm deep, was fabricated. The tablet was mounted into the holder as described before. The sample was scanned from 10 to 35° 2θ. In tablets containing CBZ and microcrystalline cellulose, the presence of the latter interfered with some lines of CBZ. Therefore only 15 lines of CBZ were used for quantitative purposes. However, in tablets composed of CBZ and starch, 24 lines of CBZ were used for quantitative analyses (Table I).

Long- and Short-Term Instrumental Drift. The quantitative nature of the work required us to detect and correct for any short- and long-term instrumental drift. Several oxide powders are available from the National Institute of Standards and Technology which can be used for checking the intensity response of X-ray diffractometers. We used ceric oxide to check for long-term instrumental drift. The powder was filled into an aluminum holder with a central cavity 15 × 15 × 1.5 mm. At regular intervals, the 111 line of ceric oxide was scanned at increments of 0.01° from 27.60 to 29.30° 2θ. Counts were accumulated for 5 sec at each step. The area of the peak was determined by integrating over the angular range of 27.877 to 29.172° 2θ. The coefficient of variation of all such samples pooled together was 1.7%. Therefore the long-term instrumental drift was assumed to be small enough not to require any correction. There was no measurable short-term instrumental drift during the time of analysis of each sample.

RESULTS AND DISCUSSION

The powder X-ray diffraction pattern of LC was identical to that of lithium carbonate reported in the Powder Diffraction File (7). Though two polymorphic forms of LC had been proposed earlier, only one form of LC is listed in the crystallographic literature, thus suggesting that the other form is uncommon (8). The powder X-ray diffraction pattern of CBZ was identical to that of both β-carbamazepine reported in the Powder Diffraction File (9) and the USP Car-

bamazepine Reference Standard (1). Though CBZ can exist in different polymorphic forms, earlier studies had confirmed that the sample used consisted only of the β form and was not a mixture of polymorphs (5). Samples of LC and CBZ when heated on the TGA showed no detectable weight loss, suggesting the absence of both physically and chemically bound water.

The weight loss on drying starch was 8.53 ± 0.47% (mean ± SD; $n = 3$). The percent weight loss observed in the TGA was 9.05 ± 0.22. In case of microcrystalline cellulose, the weight loss on drying was 3.33 ± 0.31%, while the TGA revealed a percent weight loss of 3.18 ± 0.19. The experimentally observed weight losses agreed with the water contents of starch and microcrystalline cellulose, reported to be 8.9 and 3.0% (w/w), respectively (10,11).

The theoretical basis of quantitative powder X-ray diffractometry (2,3) was discussed briefly in an earlier publication (5). The final intensity equation, in a two-component mixture, is expressed as

$$\frac{I_{i1}}{(I_{i1})_0} = \frac{x_1\mu_1^*}{x_1(\mu_1^* - \mu_2^*) + \mu_2^*} \quad (1)$$

where I_{i1} is the intensity of line i of component 1 in a powder mixture, x_1 is the weight fraction of 1, $(I_{i1})_0$ is the intensity of line i of a sample consisting of only 1, and μ_1^* and μ_2^* are, respectively, the mass absorption coefficients of 1 and 2. In order to use this equation, the mass absorption coefficients of LC, CBZ, microcrystalline cellulose, and starch had to be calculated. The mass absorption coefficient of a substance is simply the weighted average of the mass absorption coefficients of its constituent elements (12). The water content of microcrystalline cellulose (close to 3%,w/w) was small enough to be considered negligible in mass absorption coefficient calculations. Since the starch contained a higher percentage of water, the mass absorption coefficient calculation was based on the assumption that the sample contained 9% (w/w) water. The mass absorption coefficients of LC, CBZ, microcrystalline cellulose, and starch were calculated to be 8.36, 5.21, 6.16, and 6.53 cm^2/g (CuKα radiation), respectively (13).

In order to experimentally determine $(I_{i1})_0$, the integrated intensities of the appropriate lines were determined in tablets made up only of the active ingredient (LC or CBZ) and the intensity values were summed up. The sum of the integrated intensities of the same lines was also determined in the mixtures containing different weight fractions of the active ingredient and the excipient. This permitted the experimental determination of the intensity ratio as a function of the weight fraction of the active ingredient in the tablet.

For example, $(I_{i1})_0$ was obtained by summing up the integrated intensities of the eight lines of LC (Table I) in tablets containing only LC. The sum of the integrated intensities of the same eight lines of LC was also determined in tablets containing LC and microcrystalline cellulose. This enabled the experimental determination of the intensity ratio as a function of the weight fraction of LC in the tablet. In the tablets containing CBZ and microcrystalline cellulose, the amorphous halo of microcrystalline cellulose interfered with the lines of CBZ in the 2θ range of 15.5 to 24.2°. Therefore the lines in this angular range could not be used in the quantitative analysis (Fig. 1). Fifteen lines of CBZ were chosen

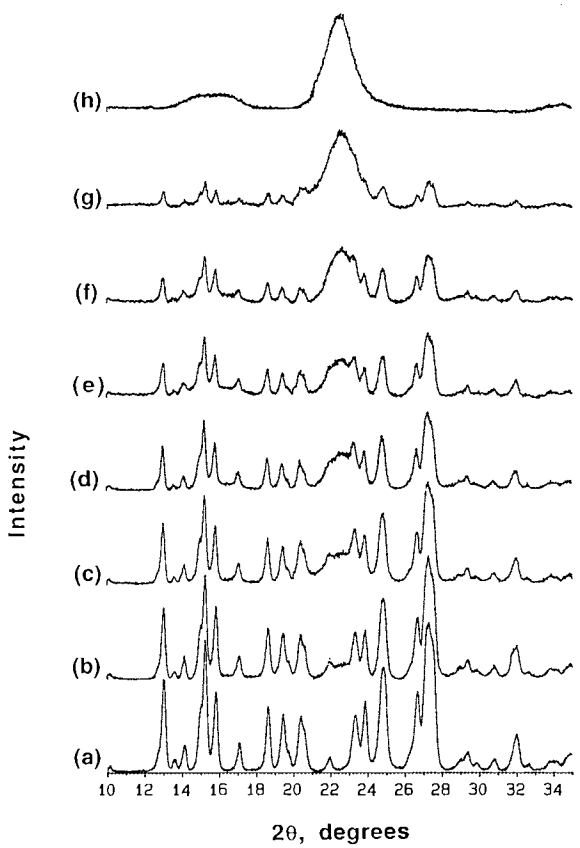

Fig. 1. The stacked plot of the background subtracted X-ray diffraction patterns of CBZ tablets (a), microcrystalline cellulose tablets (h), and tablets containing different weight fractions of CBZ and microcrystalline cellulose. The weight fraction of CBZ in the mixtures were: 0.85 (b), 0.75 (c), 0.60 (d), 0.50 (e), 0.40 (f), and 0.25 (g).

and the integrated intensities of these lines were summed up. The *d*-spacings of these lines are given in Table I. In the tablets containing CBZ and starch, the few, very weak, amorphous halos exhibited by starch appeared to have no effect on the intensities of the lines of CBZ. Therefore 24 lines of CBZ, listed in Table I, were used for quantitation. The intensity ratio is expressed as $I_{i1}/(I_{i1})_0$ in Eq. (1). Since we were summing up the intensities of several lines, the intensity ratio was expressed as I/I_0 in Figs. 2–4.

The data points in Fig. 2 were the experimentally determined intensity ratios of the LC–microcrystalline cellulose and CBZ–microcrystalline cellulose systems. The lines in the figure were based on theoretical calculations [Eq. (1)]. There was a good agreement between the theoretical and the experimental intensity measurements. In the CBZ–starch system, good agreement between the theoretical and the experimentally observed intensity ratios was observed only when the weight fraction of CBZ in the mixture was ≥0.4 (Fig. 3).

Figures 2 and 3 were based on Eq. (1). This equation would have yielded a linear relationship between the intensity ratio, $I_{i1}/(I_{i1})_0$, and the weight fraction of the unknown component (x_1) only when the mass absorption coefficients of the unknown component and the matrix were the same. This would have been an uncommon occurrence. The modification of Eq. (1) yielded Eq. (2).

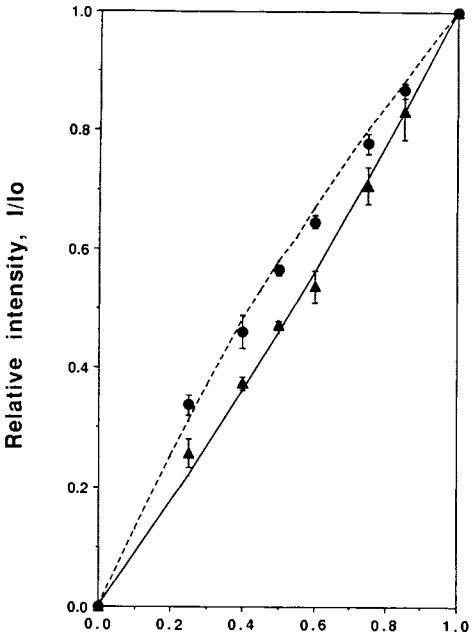

Fig. 2. The relative intensities of the sum of eight lines of LC as a function of the weight fraction of LC in tablets containing LC and microcrystalline cellulose (●- - -●) and the relative intensities of the sum of 15 lines of CBZ as a function of the weight fraction of CBZ in tablets containing CBZ and microcrystalline cellulose (▲——▲). The lines were based on theoretical values while the data points were experimental measurements. Error bars indicate standard deviations (n = 3).

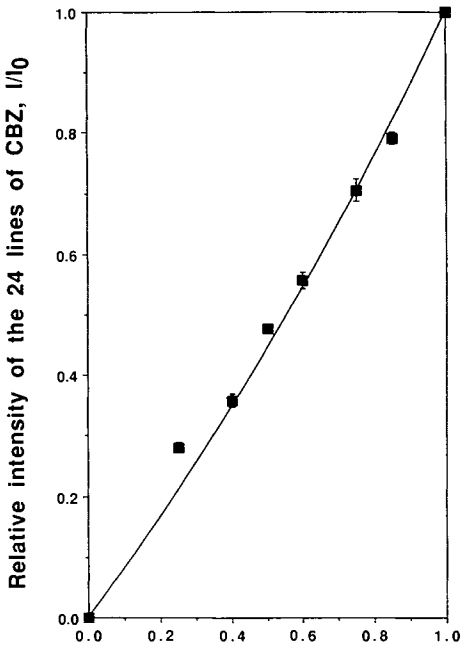

Fig. 3. The relative intensities of the sum of 24 lines of CBZ as a function of the weight fraction of CBZ in tablets containing CBZ and starch. The line was based on theoretical values while the data points were experimental measurements. Error bars (shown whenever larger than the symbols denoting the points) indicate standard deviations (n = 3).

$$\frac{I_{i1}}{(I_{i1})_0} = \frac{\mu_1^*}{\mu_1^* - \mu_2^*} - \left(\frac{\mu_1^*\mu_2^*}{\mu_1^* - \mu_2^*}\right)\frac{1}{x_1(\mu_1^* - \mu_2^*) + \mu_2^*} \quad (2)$$

A plot of $I_{i1}/(I_{i1})_0$ as a function of $1/[x_1(\mu_1^* - \mu_2^*) + \mu_2^*]$ will result in a straight line. The slope and intercept on the y axis of the line will be $-\mu_1^*\mu_2^*/(\mu_1^* - \mu_2^*)$ and $\mu_1^*/\mu_1^* - \mu_2^*$, respectively. It is possible to calculate the intensity ratio, $I_{i1}/(I_{i1})_0$, as a function of $1/[x_1(\mu_1^* - \mu_2^*) + \mu_2^*]$. For the LC tablets, the line in Fig. 4 was based on the calculated intensity ratios, while the data points were experimental measurements. The equation of the line was $y = 3.83 - 23.6x$. Such a line, obtained by substituting values of μ_1^*, μ_2^*, and x_1 into Eq. (2), is hereafter referred to as the *calculated line*. The equation of the line obtained by linear regression of the experimental data was $y = 3.61 - 22.1x$ ($r^2 = 0.996$). Such a line, obtained on the basis of experimental data, is hereafter referred to as the *experimental line*. For the CBZ tablets containing microcrystalline cellulose, the equation of the *calculated line* was $y = -5.48 + 33.8x$ (Fig. 4). The equation of the line obtained by linear regression of the experimental data (the *experimental line*) was $y = -5.36 + 33.1x$ ($r^2 = 0.997$). For the CBZ tablets containing starch, the *calculated line* was $y = -3.95 + 25.8x$ (Fig. 4). The equation of the *experimental line* was $y = -3.85 + 25.3x$ ($r^2 = 0.997$). We had earlier seen that when the weight fraction of CBZ was 0.25, there was a poor agreement between the experimental and the theoretical intensity ratios (Fig. 3). Therefore this data point was omitted from the linear regression calculation.

From the experimentally observed intensity ratio, the weight fraction of the drug in the tablets was calculated using both the *calculated* and the *experimental lines*. This permitted the calculation of the relative error for each determination (Fig. 5). The relative error, expressed as a percentage, is given by the expression

$$\frac{(\text{observed value} - \text{true value}) \times 100}{\text{true value}} \quad (3)$$

Figure 5 contains the relative error in the determination of content of LC and CBZ in the tablets. For the LC tablets, the results based on the use of the *calculated line* for error calculations indicated that when the weight fraction of LC in the tablets was $\geq$0.25, the relative error was always positive (Fig. 5a). However, much better distribution of the relative error was seen when the results were plotted based on the *experimental line* (Fig. 5b). This suggested that for determining the weight fraction of LC in unknown tablets, the use of the *experimental line* was desirable. The highest value of the relative error was 11.8%.

When similar studies were carried out on CBZ tablets, the weight fraction of CBZ determined using the *calculated* and *experimental lines* showed excellent agreement. Figure 5 contains the relative error in these determinations for the CBZ tablets containing microcrystalline cellulose and starch. In each case, a and b present the results of the error calculations based on the use of the *calculated line* and the

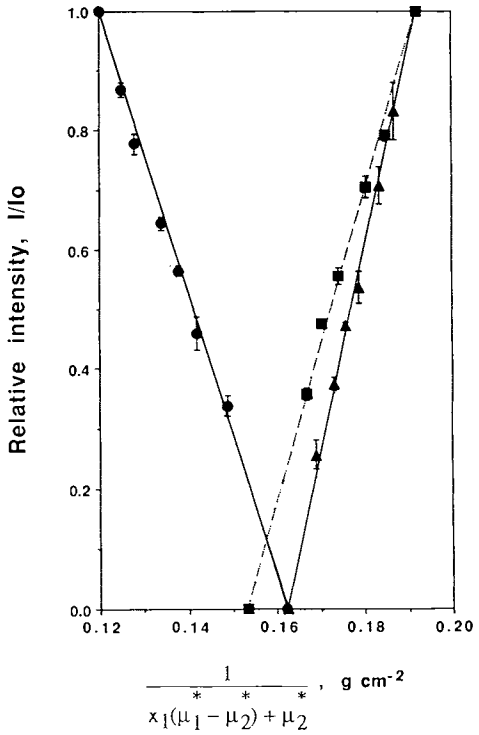

Fig. 4. The relative intensities of the sum of the lines of: (a) LC in tablets containing LC and microcrystalline cellulose (●——●), (b) CBZ in tablets containing CBZ and microcrystalline cellulose (▲——▲), and (c) CBZ in tablets containing CBZ and starch (■- - -■) as a function of $1/[x_1(\mu_1^* - \mu_2^*) + \mu_2^*]$. The lines were based on theoretical values, while the data points were experimental measurements.

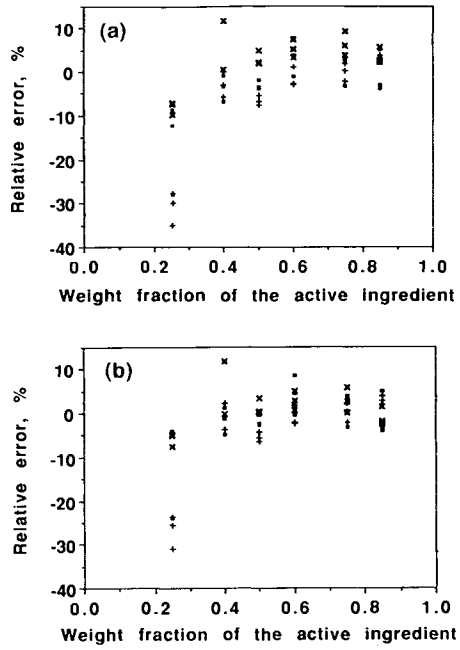

Fig. 5. The relative error in the determination of content of LC in the tablets (X), CBZ in the tablets containing CBZ and microcrystalline cellulose (■), and CBZ in the tablets containing CBZ and starch (+). (a) Use of the *calculated line* for error calculations. (b) Use of the *experimental line* for error calculations.

experimental line, respectively. The relative error values determined using the *calculated line* and the *experimental line* were in close agreement. When the weight fraction of CBZ in the tablets was between 0.40 and 0.85, the relative error was less than 10%. Therefore the use of the X-ray method in these systems was reliable only when the weight fraction of CBZ in the tablets was ≥0.4. Since there was excellent agreement in the weight fraction of CBZ determined using the *calculated* and *experimental line*, the composition of the unknown tablet in these systems could be determined using the *calculated line*. In other words, a standard curve based on known tablet compositions (i.e., *experimental line*) does not appear to be necessary for these two systems.

Compression of a solid can cause it to undergo a polymorphic transformation (14). However, the X-ray patterns of the compressed samples and the uncompressed powders were identical in the case of both LC and CBZ. Therefore it was concluded that LC and CBZ do not undergo polymorphic transformation when compressed to pressures of 136 and 90 MPa, respectively. Similarly, LC when compressed in the presence of microcrystalline cellulose and CBZ when compressed in the presence of microcrystalline cellulose and starch did not appear to undergo any polymorphic transformations.

Errors in Quantitative Powder X-Ray Diffractometry

The major sources of error in quantitative powder X-ray diffractometry were evaluated.

Particle size. Microscopic examination of LC and CBZ revealed irregularly shaped crystals. The longest dimensions of particles of LC and CBZ were measured microscopically. More than 97% of the particles of LC were ≤10 μm in size. The remaining particles were greater than 10 μm and less than 13 μm in size. Microscopic examination of CBZ revealed that a significant fraction of the particles was greater than 10 μm in size. After grinding for 5 min in a ball mill, all the examined particles were less than 10 μm in size. Therefore CBZ was ground for 5 min in a ball mill before it was used. The microcrystalline cellulose and starch were reported to have an average particle size of 20 and 15 μm, respectively (10,11).

Compression is known to cause preferred orientation of particles. However, when compressed to a certain pressure, if particles tended to orient in only one specific manner, then the variability in the peak areas should be small on replicate analyses. The coefficients of variation (CV) of the integrated intensities of the lines of LC listed in Table I were determined in tablets wherein the weight fractions of LC were 1.00, 0.85, 0.60, and 0.25. The highest CV value observed was 6.1%. Similar studies were conducted on CBZ tablets containing microcrystalline cellulose or starch. The CV of the intensity of all the lines of CBZ listed in Table I was determined in tablets wherein the weight fractions of CBZ were 1.00, 0.85, 0.60, and 0.25. These results showed that in most instances the CV values were less than 10% (88 out of a total of 96 observations) and in a few instances they were above 12% (5 out of 96).

Extinction. The diffracted intensity from substances crystallizing with a high degree of perfection decreases when the crystallites are larger than 10–15 μm. This is known as

primary extinction (12). In particles smaller than this size, errors due to primary extinction are negligible. Particles of LC and CBZ were less than 15 μm in size. Moreover, these crystals were unlikely to have a very high degree of perfection. Primary extinction effects in microcrystalline cellulose and starch need not be considered since their X-ray powder pattern indicates that they do not have a high degree of perfection.

Microabsorption. The accuracy of intensity measurements can also be affected by a phenomenon called microabsorption. Let us consider a powder mixture of two phases, α and β. The problems of microabsorption are negligible if the following conditions are met: (i) $\mu_\alpha = \mu_\beta$, where μ is the linear absorption coefficient; and (ii) both phases have the same particle size or consist of extremely fine particles (12). The linear absorption coefficient of a substance is obtained by multiplying the mass absorption coefficient by the density of the substance (3). The linear absorption coefficient values of both LC and CBZ were close to that of microcrystalline cellulose and starch (Table II). Based on the earlier discussion of particle size, we can reasonably assume that all the phases consist of fine particles. It is interesting that Alexander and Klug (2) performed quantitative analysis of binary mixtures wherein the constituents had very different linear absorption coefficient values. Still the experimentally observed intensity ratios were in excellent agreement with the theoretical intensity ratios.

The maximum acceptable particle size in quantitative X-ray analysis can be calculated according to the formula of Brindley (15). This formula assumes that absorption of X-rays within each particle is 1% and calculates the maximum particle size for satisfactory averaging of the absorption process.

$$t_{max} = \frac{1}{100\bar{\mu}} \quad (4)$$

Here t_{max} is the maximum acceptable particle size and $\bar{\mu}$ is the linear absorption coefficient of the material composing the powder. The maximum acceptable particle size of the various compounds was calculated (Table II). From among the four compounds, the sizes of the particles of LC and CBZ were close to or below the maximum size acceptable, while those of the excipients were above the maximum acceptable size. Since the observed intensity ratios were in good agreement with the calculated intensity ratios, it is likely that the particle size[3] of microcrystalline cellulose and starch had a small effect, if any, on the experimental intensity ratios. Tablets containing 50% (w/w) CBZ were also prepared using larger particles of microcrystalline cellulose as the excipient. This sample of microcrystalline cellulose (Avicel PH-101) had an average particle size of 50 μm. The experimental intensity ratio, I/I_0, was observed to be 0.455 ± 0.033 (mean ± SD; $n = 3$), which was in excellent agreement with the calculated intensity ratio of 0.458. These results confirmed the earlier finding that the rigorous limitations on particle size [Eq. (4)] were not applicable to microcrystalline cellulose. This observation has a lot of practical importance since the particle size of many of the widely used excipients will be substantially greater than that acceptable according to Eq. (4).

[3] We are referring to the size of the particles before they were compressed. The effect of compression on the particle size is not known.

Table II. The Mass Absorption Coefficient (μ*), Density (ρ), Linear Absorption Coefficient (μ), and Maximum Acceptable Particle Size (t_{max}) of the Compounds

	μ* (cm^2/g)	ρ (g/cm^3)	μ (cm^{-1})	t_{max} (μm)
Lithium carbonate	8.36	2.11	17.6	5.67
Carbamazepine	5.21	1.34	6.98	14.3
Microcrystalline cellulose	6.16	1.57	9.67	10.3
Starch	6.53	1.50	9.80	10.2

Limitations of the Quantitative X-Ray Technique

The analytical technique developed will be applicable only under limited conditions. The first and foremost requirement is that the active ingredient be crystalline. In order for this method to be applicable, it also appears that the active ingredient should form a substantial weight fraction of the tablet. In the systems studied, the weight fraction of lithium carbonate must be ≥0.25 and the weight fraction of carbamazepine must be ≥0.4.

It is possible that the X-ray patterns of the active ingredient and the substances constituting the matrix interfere with one another. Our studies so far have been restricted to the use of excipients which are not highly crystalline. Moreover, the tablet composition so far has been very simple, consisting of the active ingredient and one excipient.

For the experimental determination of the intensity ratio, $I_{i1}/(I_{i1})_0$ [Eqs. (1) and (2)], it is necessary to compress tablets containing only the active ingredient under the same experimental conditions as the "unknown" tablet. Finally, the sources of error in quantitative powder X-ray diffractometry will have to be carefully considered during the development of the analytical method.

The unique advantage of the method is that it permits quantitative analysis of the active ingredient in intact tablets by a nondestructive technique. The sample can be prepared for analysis in a short time by an extremely simple procedure. Morever, the analytical procedure will lend itself to considerable automation, resulting in further savings in operator time.

One possible application of the technique will be to monitor the drug content in individual tablets during accelerated stability studies. Studies along these lines are currently under progress.

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