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Quantitative analysis of the active ingredient in a multi-component tablet formulation by powder X-ray diffractometry

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Summary

A powder X-ray diffraction technique has been developed for the quantitative analysis of the active ingredient in intact tablets. Carbamazepine (CBZ) was the model drug and the other tablet ingredients were microcrystalline cellulose, starch, stearic acid and silicon dioxide. The integrated intensities of 21 X-ray lines of CBZ were used for the quantitative analysis. The ratio of the intensities of the X-ray lines in these tablets to the intensity of the same lines in tablets containing only CBZ was calculated as a function of the CBZ weight fraction. Such a calculation was based on the mass absorption coefficients of the tablet ingredients. These ratios were also experimentally determined in prepared tablets wherein the weight fraction of CBZ ranged from 0.51 to 0.69. There was a good agreement between the calculated and experimental intensity ratios. The relative error in the determination of CBZ was less than 10%. Small changes either in the compression pressure or in the tablet composition did not affect the validity of the assay method.

Introduction

An X-ray diffractometric method was recently developed for the quantitative analysis of the active ingredient in intact tablets (Suryanarayanan and Herman, 1991). The technique was nondestructive and permitted the analyses of intact tablets. Because of the preliminary nature of the study, only very simple systems were studied. The tablets contained the active ingredient and only one excipient. Lithium carbonate and carbamazepine (CBZ) were used as the model inorganic and organic drugs, respectively.

The object of the present investigation was to evaluate the validity of the technique in complex tablet formulations. Formulations were prepared which contained in addition to CBZ, microcrystalline cellulose, starch, stearic acid and silicon dioxide. These formulations were subjected to quantitative powder X-ray diffractometry. The validity of the assay method was checked following small changes in the tablet composition and in the compression pressure.

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Papariello et al. (1964) had attempted to use X-ray diffractometry for the quantitative analysis of a tablet formulation. This study was of a preliminary nature and the quantitation was based on the intensity (peak height) of one line of the active ingredient. It is now well recognized that in the measurement of diffraction line intensity, the integrated line intensity (area under the curve of the peak) and not the maximum intensity must be measured (Cullity, 1978). Variations in particle size and microstrain can cause large variations in line shape. However, these variations will not affect the integrated intensity. The availability of computer software has not only simplified the determination of the integrated peak intensity but has also permitted automatic background subtraction. As a result, the intensities of numerous X-ray lines of a compound can be used for quantitative analysis. This aids to minimize some of the errors associated with quantitative X-ray diffractometry.

Materials and Methods

Materials

CBZ [assay ($C_{15}H_{12}N_2O$) > 99%] was obtained from Sigma Chemical Co. (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-101, FMC Corp., Philadelphia, PA), starch (STA-Rx, A.E. Staley Manufacturing Co., Decatur, IL), and silicon dioxide (CAB-O-SIL, Cabot Corp., Tuscola, IL) were used as received. Stearic acid (Fisher Scientific, Fair Lawn, NJ) was passed through a 100-mesh sieve before it was used.

Weight loss on drying

The weight loss on drying of starch and microcrystalline cellulose was determined according to the procedure outlined in the United States Pharmacopeia (USP XXII, 1989). The starch was heated at 120°C for 4 h and the microcrystalline cellulose was heated at 105°C for 3 h.

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. The CBZ was heated from 30 to 175°C while the microcrystalline cellulose and starch were heated from 30 to 120°C.

Preparation of tablets

Tablets were prepared with CBZ weight fraction ranging from 0.49 (170 mg per tablet) to 0.61 (230 mg per tablet). As mentioned earlier, the excipients in the formulation were microcrystalline cellulose, starch, stearic acid and silicon dioxide (King and Schwartz, 1985). The silicon dioxide (0.5% w/w, 1.7 mg) and stearic acid (2.0% w/w, 6.7 mg) content per tablet was maintained constant in all the tablets. The rest of the tablet was made up of microcrystalline cellulose and starch. Unless otherwise mentioned, the weight ratio of microcrystalline cellulose to starch

TABLE 1

Compositions (mg / tablet) of the different carbamazepine formulations

Ingredients	Regular tablets	Tablets with 'high' microcrystalline cellulose content	Tablets with 'high' starch content
(1)	(2)	(3)	(4)
Carbamazepine	200	200	200
Microcrystalline cellulose	66.7	75.0	56.3
Starch	58.3	50.0	68.8
Stearic acid	6.7	6.7	6.7
Silicon dioxide	1.7	1.7	1.7

was maintained constant at 1.14. The composition of one representative formulation is given in Table 1 in column 2. The appropriate amounts of CBZ and the excipients were mixed and 333 mg of the mixture was accurately weighed and compressed in a hydraulic press (Fred C. Carver, Menomonee Falls, WI) to a pressure of 90 MPa and held for 1 min. The tablets were 11.2 mm in diameter and 3.2 mm thick.

X-ray diffractometry

An aluminum sample holder with a circular central cavity, 11.3 mm in diameter and 3.5 mm deep, was fabricated. Two small pieces of molding clay were put at the bottom of the holder, the tablet was dropped into the cavity and using a flat glass slide, the tablet was gently pressed down until the holder surface and the tablet surface were coplanar. The tablets were exposed to CuKα radiation (40 kV, 30 mA) in the step-scan mode with increments of 0.02° 2θ, in a wide-angle X-ray diffractometer (model D500, Siemens). The Bragg-Brentano focusing geometry was used, with a 1° incident aperture slit, 0.15° detector slit and a scintillation counter as the detector. Counts were accumulated for 1 s at each step over the angular range of 10–35° 2θ. 21 lines of CBZ were used in the quantitative analysis and Table 2 lists the Miller indices of these lines. The angular range over which the integration was carried out to obtain the intensities of these lines is also given in Table 2. After obtaining the powder X-ray diffraction pattern, automatic subtraction of the background was performed using the software in the instrument (X-ray Diffraction Software Manual, 1989). The intensity values of all the lines were summed up.

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. The use of a Standard Reference Material from the National Institute of Standards and Technology revealed that the long-term instrumental drift was small enough to be assumed negligible (Suryanarayanan and Herman, 1991). In addition, tablets containing only CBZ were periodically subjected to X-ray studies and the intensities of the lines listed in Table 2 were obtained and summed up. The coefficient of variation of all such samples pooled together was 3.1% (n = 24). This confirmed that the long-term instrumental drift was negligibly small. There was no measurable short-term instrumental drift during the time of analysis of each sample.

TABLE 2

Lines of carbamazepine used in the quantitative analysis

d spacing (Å)	Miller indices	Integration angles (°), 2θ
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
4.74	−211	18.02–18.96
4.55 4.49	211 021	18.96–19.92 [a]
4.35 4.30	220 −121	19.92–21.06 [a]
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.

Effect of formulation variables

It was desired to check the validity of the analytical method following small changes in the tablet formulation. Therefore, tablets were prepared wherein the relative amounts of microcrystalline cellulose and starch were altered. Table 1 contains the formulation details.

Effect of compression pressure

Tablets containing 200 mg of CBZ per tablet were prepared and compressed at pressures ranging from 67.7 to 112.9 MPa. The composition of the tablets is given in Table 1 in column 2.

Results and Discussion

The powder X-ray diffraction pattern of CBZ was identical to that of both β-CBZ reported in the Powder Diffraction File (1989) and the United States Pharmacopeia CBZ Reference Standard (USP XXII, 1989). Although 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 (Suryanarayanan, 1989). When CBZ was heated on the TGA no detectable weight loss occurred. This suggested the absence of both absorbed water and water of crystallization.

The weight loss on drying starch (mean $\pm$ SD; $n = 3$) was $9.92 \pm 0.23\%$. The percent weight loss observed in the TGA was 9.41 ± 0.25. In the case of microcrystalline cellulose, the weight loss on drying was $2.80 \pm 0.27\%$ while the TGA revealed a percent weight loss of 2.92 ± 0.23.

The theoretical basis of quantitative powder X-ray diffractometry was developed by Alexander and Klug (Alexander and Klug, 1948; Klug and Alexander, 1974). Although a solid mixture may be composed of several components, it was regarded to be composed of just two components: component 1, which was the unknown, and component 2 (the sum of the other components), which was designated the matrix. In our experimental system, CBZ was the unknown component and the excipients in the formulation formed the matrix. The final intensity equation was expressed as:

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

where I_{i1} denotes the intensity of line i of component 1 in a powder mixture where x_1 is the weight fraction of 1, $(I_{i1})_0$ represents the intensity of line i of a sample consisting of only 1, and μ_1^* and μ_2^* are the mass absorption coefficients of 1 and 2, respectively. To use Eqn 1, the mass absorption coefficients of CBZ, microcrystalline cellulose, starch, stearic acid and silicon dioxide 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 (Cullity, 1978). The water content of microcrystalline cellulose (close to 3% w/w) was low 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 9.9% w/w water. The mass absorption coefficients of CBZ, microcrystalline cellulose, starch and stearic acid were calculated to be 5.21, 6.16, 6.57 and 4.85 cm^2/g (CuKα radiation), respectively (Macgillavry and Rieck, 1983). The amounts of microcrystalline cellulose and starch present per tablet depended on the CBZ content of the tablet. Therefore, the mass absorption coefficient of the matrix depended on the tablet composition. In the tablets with the lowest weight fraction of the matrix (matrix weight fraction, 0.31; CBZ weight fraction, 0.69), the mass absorption coefficient of the matrix was calculated to be 6.16 cm^2/g. In the tablets with the highest weight fraction of the matrix (matrix weight fraction, 0.49), the mass absorption coefficient of the matrix was calculated to be 6.23 cm^2/g. Therefore, the mass absorption coefficient was calculated for an intermediate composition (matrix weight fraction, 0.40) and found to be 6.19 cm^2/g. This value was used in all the calculations. Since the tablets contained only 0.5% w/w silicon dioxide, its presence was not considered in the mass absorption coefficient calculations.

The stacked plot of the X-ray diffraction patterns in Fig. 1 was obtained from the tablets of different compositions. In order to determine $(I_{i1})_0$ experimentally, the integrated intensities of the 21 lines listed in Table 2 were determined in tablets made up only of CBZ and the intensity values were summed up. The sum of the integrated intensities of the same lines was also determined in the tablets containing different weight

fractions of CBZ and the excipients. This permitted the experimental determination of the intensity ratio as a function of the weight fraction of CBZ in the tablet. There was a good agreement between the theoretical and experimental intensity ratios. Eqn 1 would have yielded a linear relationship between the intensity ratio, $(I_{i1})/(I_{i1})_0$, and the weight fraction of the unknown component only when the mass absorption coefficients of the unknown component and the matrix were the same. This was not the case in our experimental system. Eqn 1 was modified to Eqn 2 (Suryanarayanan and Herman, 1991) so that a plot of $I_{i1}/(I_{i1})_0$ as a function of $1/[x_1(\mu_1^*-\mu_2^*)+\mu_2^*]$ resulted in a straight line (Fig. 2):

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

The line in Fig. 2 was based on calculated intensity ratios while the data points were experimental measurements. The intensity ratio was expressed as $(I_{i1})/(I_{i1})_0$ in Eqns 1 and 2. Since we were summing up the intensities of several

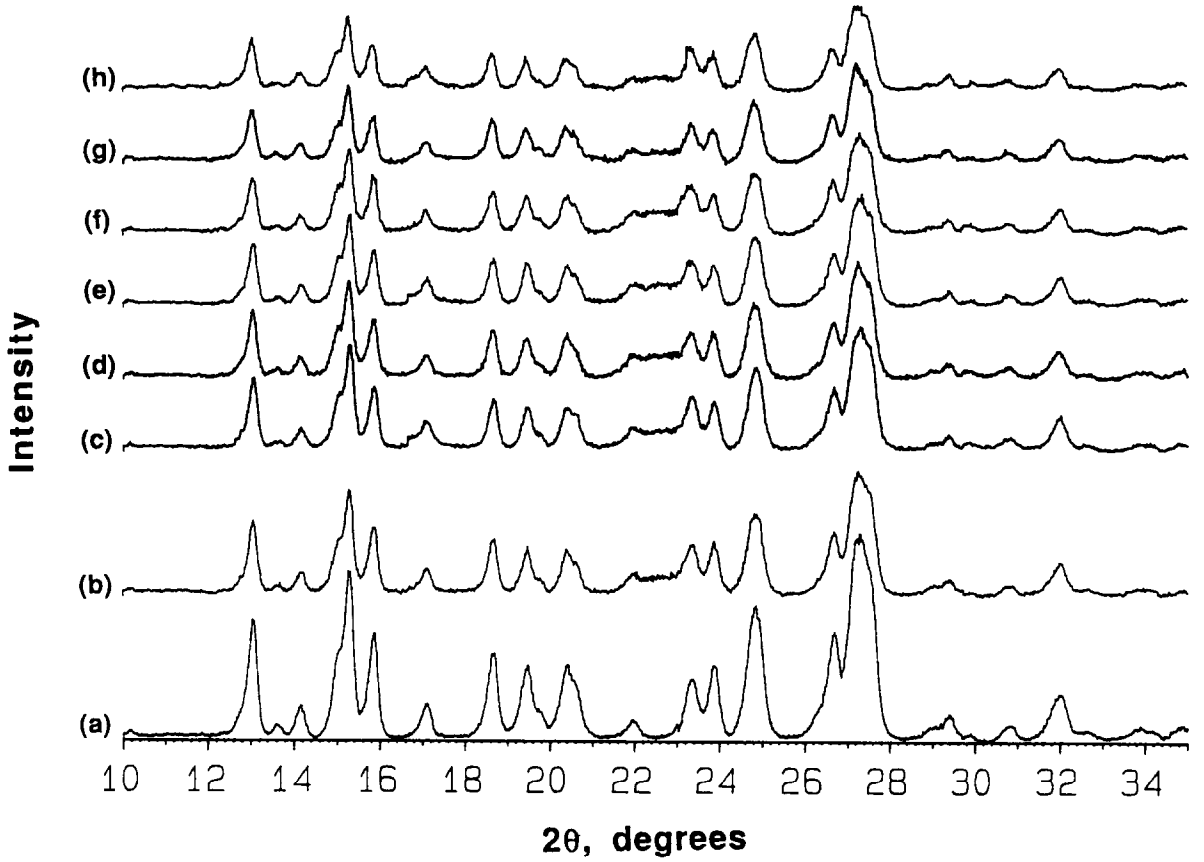

Fig. 1. Stacked plot of the background-subtracted X-ray diffraction patterns of tablet containing only CBZ (a) and tablets containing CBZ and the excipients (b–h). The weight fractions of CBZ in the tablets were: 0.69 (b), 0.66 (c), 0.63 (d), 0.60 (e), 0.57 (f), 0.54 (g) and 0.51 (h).

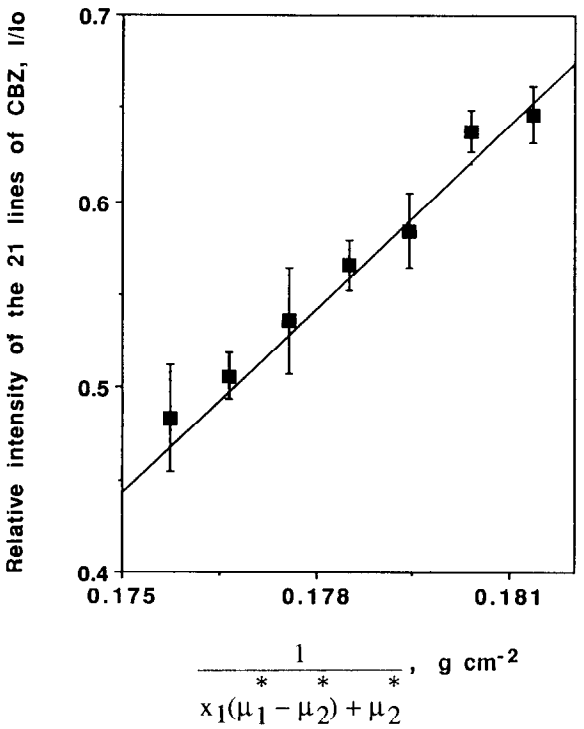

Fig. 2. Relative intensity of the sum of 21 lines of CBZ as a function of $1/[x_1(\mu_1^* - \mu_2^*) + \mu_2^*]$. The line was based on theoretical values, while the data points were experimental measurements. Error bars indicate standard deviations ($n \geq 3$).

lines, the intensity ratio was expressed as I/I_0 in Fig. 2. The equation of the line was $y = -5.32 + 32.91x$. This was obtained by substituting values of μ_1^*, μ_2^* and x_1 into Eqn 2. This line will be hereafter referred to as the calculated line. The

TABLE 3

Use of Eqn 2 to determine the weight fraction of CBZ in the tablets

Weight fraction of CBZ in the tablets	Weight fraction of CBZ (mean ± SD; $n = 3$ [a]) determined using	
	Calculated line [b]	Experimental line [c]
0.510	0.526 ± 0.029	0.512 ± 0.032
0.540	0.549 ± 0.012	0.538 ± 0.014
0.570	0.578 ± 0.028	0.570 ± 0.031
0.600	0.608 ± 0.013	0.603 ± 0.015
0.630	0.626 ± 0.010	0.622 ± 0.0021
0.660	0.676 ± 0.010	0.679 ± 0.011
0.690	0.685 ± 0.013	0.688 ± 0.016

[a] In some cases, $n > 3$.
[b] The equation of the line is: $y = -5.32 \pm 32.91x$.
[c] The equation of the line is: $y = -4.75 + 29.74x$.

equation of the line obtained by linear regression of the experimental data (hereafter referred to as the experimental line) was $y = -4.75 + 29.74x$ ($r^2 = 0.987$). From the experimentally observed intensity ratio, the weight fraction of CBZ in the tablets was calculated using both the calculated and the experimental lines (Table 3). This permitted the calculation of the relative error for each determination (Fig. 3). In Fig. 3, panels a and b contain the relative error in the determination of the CBZ content in the tablets based on the use of the calculated and the experimental lines, respectively. The relative error was less than 10%. The error values determined using the calculated

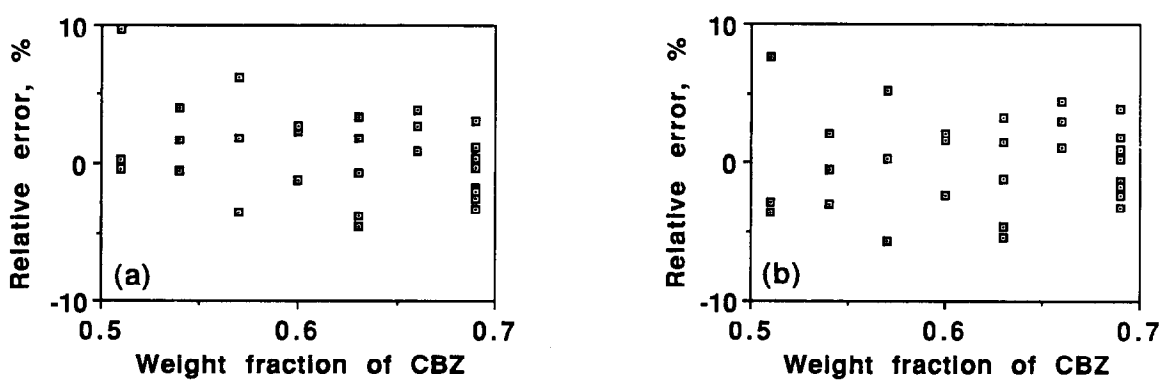

Fig. 3. Relative error in the determination of CBZ content in the tablets. (a) Use of the calculated line for error calculations. (b) Use of the experimental line for error calculations.

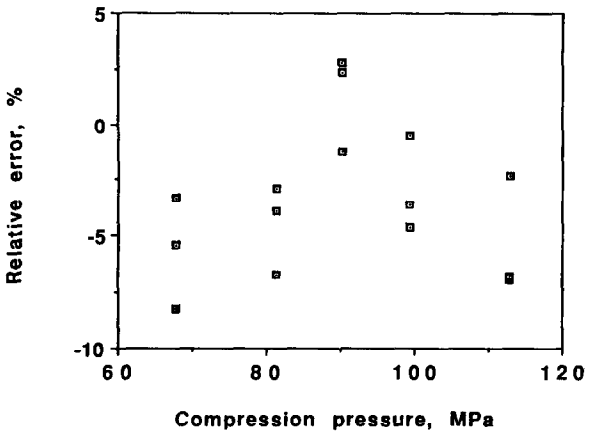

Fig. 4. Relative error in the determination of CBZ content in the tablets as a function of compression pressure. The weight fraction of CBZ in the tablets was 0.60. The composition of these formulations is given in Table 1 in column 2.

and the experimental lines were generally in close agreement. Therefore, the composition of an unknown tablet, formulated and compressed under similar conditions 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 this system.

To determine the effect of compression pressure, if any, on the intensities of the X-ray peaks, tablets containing only CBZ were prepared under different compression pressures. The sum of the integrated intensities of the 21 lines of CBZ when compressed to 81.3, 90.3 and 99.3 MPa was (mean $\pm$ SD) $4.49 \times 10^5 \pm 0.177 \times 10^5$ ($n = 3$), $4.64 \times 10^5 \pm 0.150 \times 10^5$ ($n = 24$) and $4.55 \times 10^5 \pm 0.091 \times 10^5$ ($n = 3$), respectively. There was no significant difference in intensity as a function of compression pressure as indicated by one-way ANOVA. A P value < 0.05 was considered significant. Therefore, it was concluded that small changes in compression pressure had no effect on the intensities of the lines.

The effect of compression pressure on the formulated tablets was studied in greater detail. In this case, the compression pressure ranged from 67.7 to 112.9 MPa. In each case, the intensity ratio, I/I_0, was obtained by dividing the intensity of the CBZ lines in the formulated tablets, by the intensity of the same lines in pure CBZ tablets compressed to 90.3 MPa. From the experimental intensity ratio, the weight fraction of CBZ in the tablets was determined using the calculated line. Fig. 4 contains the relative error as a function of the compression pressure. At all the compression pressures studied, the relative error was less than 10%. Therefore, small changes in compression pressure did not affect the validity of the assay method.

To study the effect of formulation variables, the relative amount of microcrystalline cellulose and starch was altered in the formulations (Table 1). The intensities of the lines of CBZ (mean $\pm$ SD; $n = 3$) in the regular tablets, the tablets with 'high' microcrystalline cellulose and the tablets with 'high' starch were $2.62 \times 10^5 \pm 0.062 \times 10^5$, $2.58 \times 10^5 \pm 0.071 \times 10^5$, and $2.56 \times 10^5 \pm 0.158 \times 10^5$, respectively. There was no significant difference in intensity as a function of tablet formulation as indicated by one-way ANOVA ($P < 0.05$).

Compression of a solid can cause it to undergo a polymorphic transformation. However, Lefebvre et al. (1986) had observed that compression did not cause any phase transformation of β-carbamazepine. We had also observed that the X-ray patterns of compressed and uncompressed β-carbamazepine were identical over a compression pressure range of 62–250 MPa (Suryanarayanan, 1989). The appropriate amounts of CBZ and the excipients were mixed (composition of these formulations is given in Table 1 in column 2) and the X-ray diffraction patterns were obtained before and after compression. They were identical indicating that CBZ when compressed in the presence of the excipients did not undergo any polymorphic transformation.

Errors in quantitative powder X-ray diffractometry

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 peak areas should be small on replicate analyses. The coefficient of variation (CV) of the integrated intensities of the lines of CBZ listed in Table 2 was determined in the regular tablets.

TABLE 4

Coefficient of variation (%) of the integrated intensities of the lines of CBZ

d spacing (Å)	Weight fraction of CBZ						
	0.51	0.54	0.57	0.60	0.63	0.66	0.69
6.94 6.77	6.5	3.5	4.5	2.9	3.4	1.2	5.7
6.49	4.5	2.4	3.9	5.6	8.6	3.8	7.9
6.24	6.3	1.9	1.9	2.5	6.0	2.6	4.4
5.90 5.79	6.4	5.1	4.3	1.6	2.4	1.0	0.91
5.60 5.58	7.7	16	5.1	3.7	4.3	2.6	2.8
5.18	17	24	17	27	3.4	14	3.4
4.74	8.1	10	4.7	3.4	4.6	3.8	4.0
4.55 4.49	16	3.2	4.5	6.7	5.3	6.3	11
4.35 4.30	3.8	6.1	5.7	8.6	32	3.0	13
3.59 3.57	5.2	3.8	12	4.1	8.8	6.6	8.8
3.38 3.34 3.28	9.5	1.9	6.0	5.8	2.7	1.5	0.85
2.81 2.79	1.7	3.2	1.1	5.2	2.3	5.5	2.6

The weight fraction of CBZ in these tablets ranged from 0.51 to 0.69 (Table 4). The intensity of the 5.18 Å line was found to be highly variable. This may be due to the low intensity of the line (Fig. 1). For the other lines, the CV values in most instances were less than 15% (Table 4). The other major sources of error in quantitative powder X-ray diffractometry were systematically evaluated earlier (Suryanarayanan and Herman, 1991).

Recently, we developed another X-ray diffractometric method to quantify the CBZ content in tablet formulations (Suryanarayanan, 1991). The relative error in this method was less than 4%. However, this method required grinding of the tablet into a powder followed by the addition of an internal standard. Therefore, the method was destructive.

Limitations of the technique

The analytical technique will be applicable only under limited conditions. The foremost requirement is that the active ingredient be crystalline. Secondly, for the experimental determination of the intensity ratio, $I_{i1}/(I_{i1})_0$ (Eqns 1 and 2), it is necessary to compress tablets containing only the active ingredient under the same experimental conditions as the unknown tablet. Furthermore, the X-ray diffraction patterns of the excipients should interfere minimally with that of the active ingredient. We did not face this problem for two reasons. The excipients that formed a substantial weight fraction of the matrix (starch and microcrystalline cellulose) were poorly crystalline. The crystalline excipients (stearic acid and silicon dioxide) formed such a small weight fraction of the tablet that they did not exhibit any diffraction lines. Finally, the sources of error in quantitative 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 in intact tablets by a nondestructive technique. The present study has shown the validity of the method in complex tablet formulations.

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