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X-ray powder diffraction profile fitting in quantitative determination of two polymorphs from their powder mixture

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Summary

X-ray powder diffraction profile fitting analysis has been developed to reveal the relative amounts of two prazosin hydrochloride polymorphs from their powder mixture. Diffraction profiles were measured from carefully prepared samples of a pure α-prazosin, δ-prazosin and their mixed powder having weight fractions of α-prazosin ranging from 0.5 to 10%. With the aid of mathematical profile fitting, the background intensity level of δ-prazosin and the integrated intensity of the peak caused by α-prazosin have been determined. As a result, a surprisingly good detection sensitivity of 0.5% has been reached, although the peak of α-prazosin used in determination overlapped somewhat with that of δ-prazosin. Therefore, it has been concluded that this technique is generally able to reveal relative amounts of two crystalline polymorphs from their powder mixture to a sensitivity of 0.5–1% depending on the state of peak overlapping.

Introduction

A means of controlling the consequences due to the tendency of drug substances to appear in different crystal forms is important in a variety of instances in the pharmaceutical industry. As stated (Haleblian and McCrone, 1969; York, 1983), probably every organic medical compound can exist in different polymorphic forms and the choice of proper polymorphs will determine whether the drug substance will be chemically or physically stable, whether it is readily formed into tablets and whether it results in an appropriate blood level to produce the correct pharmacological response. In addition to a review (York, 1983), several articles and reviews concerning pharmaceutical applications of polymorphs have appeared in the pharmaceutical literature (Kuhnert-Brandstatter, 1965; Rosenstein and Lamy, 1969; Mewada et al., 1973; Haleblian, 1975; Burger and Griesser, 1989).

The main analytical methods for the study of the solid-state properties of polymorphs are X-ray crystallography, differential scanning calorimetry, IR spectroscopy and NMR spectroscopy. The identification of polymorphs with these techniques is quite well established. On the other hand, the suitability of the methods for the quan-

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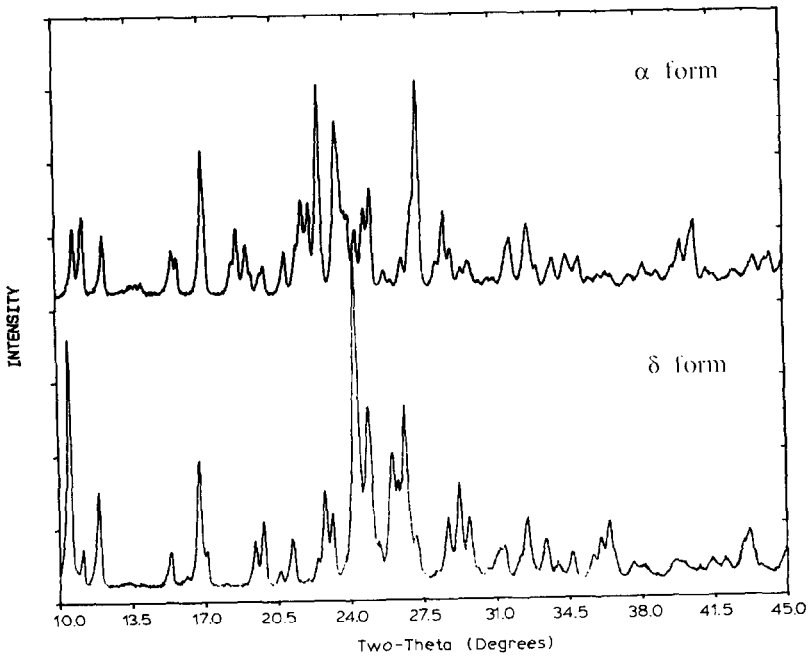

Fig. 1. X-ray powder diffraction patterns of prazosin hydrochloride; α and δ forms.

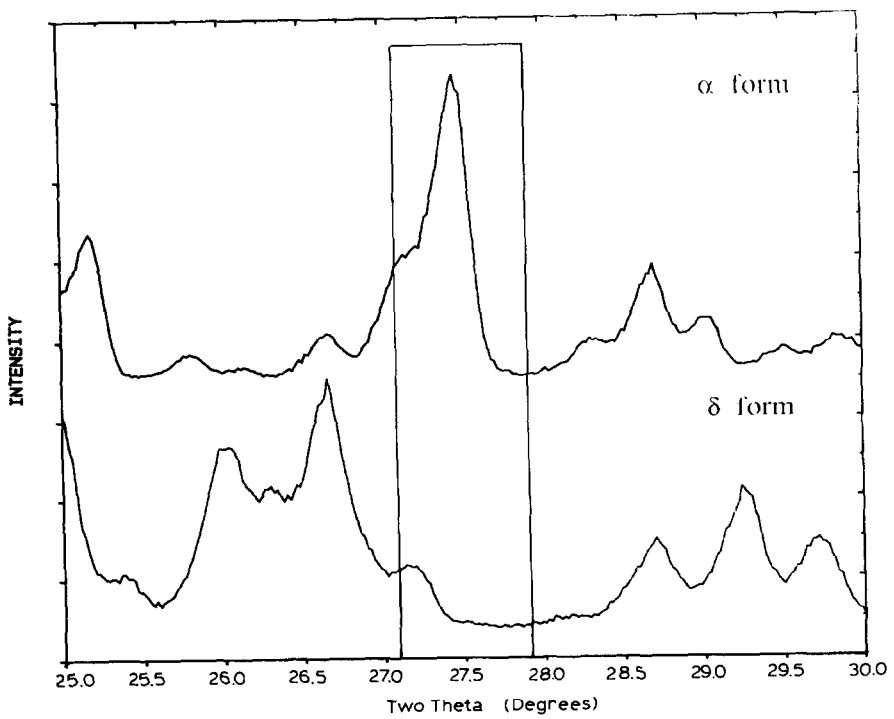

Fig. 2. Detailed strips (5 and 0.8°) of the X-ray powder diffraction patterns of prazosin hydrochloride; α and δ forms.

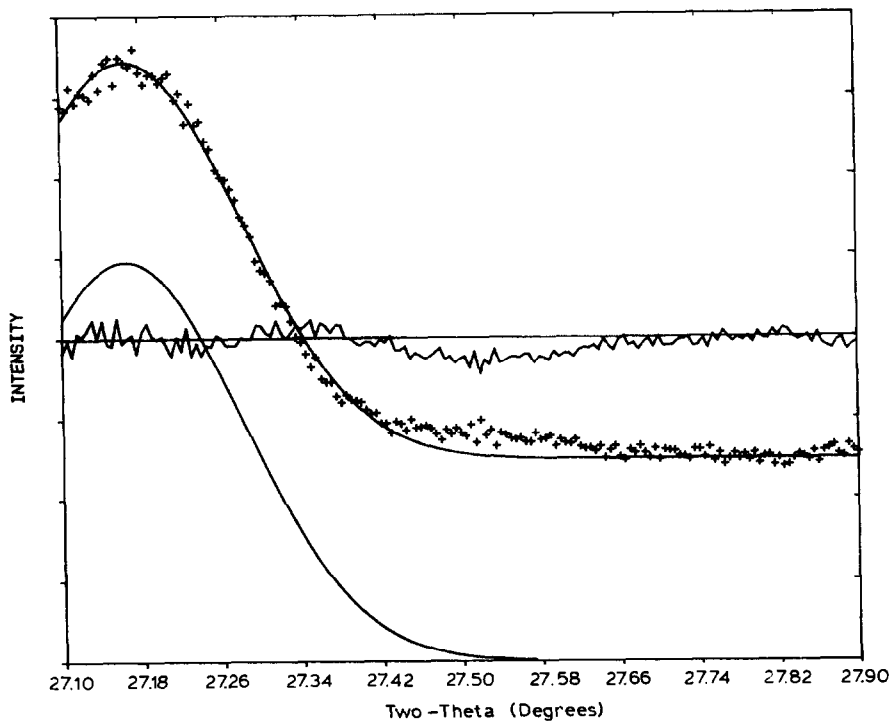

Fig. 3. Profile fitting of pure δ-prazosin as a result of an incorrect background fit.

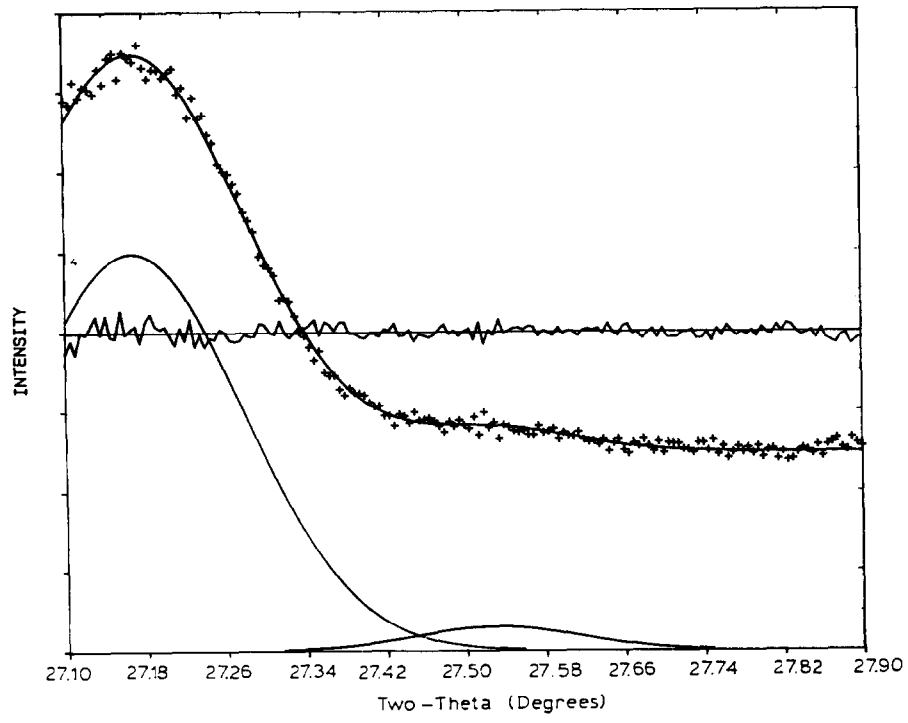

Fig. 4. Profile fitting of pure δ-prazosin as a result of a satisfactory background fit.

titative analysis of mixtures of polymorphs commonly existing in pharmaceutical raw materials has not been fully determined. This may be caused by instrument- and sample-dependent limitations which are often encountered in analysis of organic materials but not in studies of inorganic substances.

The aim of this study is to apply X-ray powder diffraction to the evaluation of the relative amounts of two polymorphs from their powder mixture. Specifically, detailed analysis of powder diffraction profiles with the aid of mathematical profile fitting will be performed with the purpose of determining the sensitivity of the method. The selected example reveals the relative amount of α-prazosin in δ-prazosin. Prazosin hydrochloride exists in at least eight different crystal forms. X-ray diffraction patterns and other characteristics of α, β, γ, δ, methanolate, anhydrate, monohydrate and polyhydrate forms have been described in two US Patents (1978, 1988). The difference in the diffraction patterns of α- and δ-prazosin is not very pronounced. Therefore, they are good testing materials for general purposes in attempts to determine the reliability of the X-ray diffraction method in the study of polymorph mixtures.

Materials and Methods

Materials

Prazosin hydrochloride samples were obtained from the supplier of raw materials, Fermion (Orion Pharmaceutica, Espoo, Finland). Samples included pure α- and δ-prazosin and weight fractions of α-prazosin in δ-prazosin as follows: 0.5, 1, 2, 5 and 10%.

For X-ray powder diffraction analysis, prazosin hydrochloride samples were mounted by loosely pressing about 500 mg of the powder into the specific cylindrical sample holder of diameter 20 mm and height about 2 mm.

Measurement of line profiles

The diffraction patterns were recorded using the X-ray powder diffraction (XRPD) facilities,

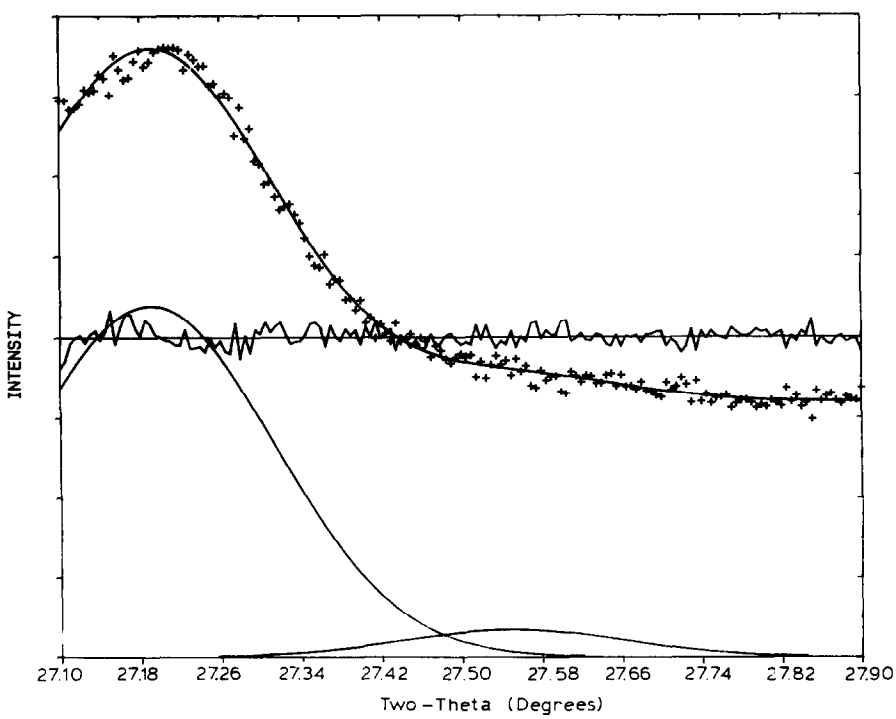

Fig. 5. Fit of α-prazosin peak obtained from the X-ray diffraction pattern of a binary mixture of α- and δ-prazosin; weight fraction of α-prazosin, 0.5%.

Siemens D 500 (Siemens AG, Karlsruhe, Germany). A copper target X-ray (wavelength 1.541 Å) tube was operated at a power of 40 kV × 40 mA. Collimation and monochromatisation of the X-ray beam were performed with a Johann-type graphite monochromator, the automatical divergence slit having a 1° entrance slit (maximum), Soller slits and a 0.05° receiving slit. The measuring range of the general patterns was 5–40° (2Θ) with a step size of 0.02° and a measuring time of 1°/min. Detailed profiles from 27.1 to 27.9° were measured using a step size of 0.005° and a measuring time of 0.1°/min.

Profile fitting procedure

In the profile fitting procedure, the program DIFFRAC 500 was applied. The program works automatically but also allows the user to specify parameters to be used in the least-squares fitting. This feature of the program was employed in the study of weak and partly overlapping peaks. In the line fitting, the user's input values were only fit function, fit range and rough estimates of peak height, width and background.

The fit functions included in the DIFFRAC 500 program are Gaussian, Cauchy, Pseudo-Voigt, Pearson VII or Split Pearson VII functions. A detailed description of the mathematical forms of those functions is available elsewhere (Müller-Goelbl, 1985). For this analysis the symmetrical Gaussian function matched very well and was the optimal choice for detailed analysis of the profiles. The mathematical presentation of the Gaussian function applied is as follows:

$$Y = I_0 \exp(-kx^2),$$

where I_0 is the peak intensity, x denotes the distance $2\Theta_i - 2\Theta_k$ from any angle $2\Theta_k$, k is $\ln 2/(a/2)^2$, and a represents the FWHM (full width at half-maximum intensity).

Calculation of the calibration curve

The net integral areas of the fitted α-prazosin profiles were plotted as a function of its weight

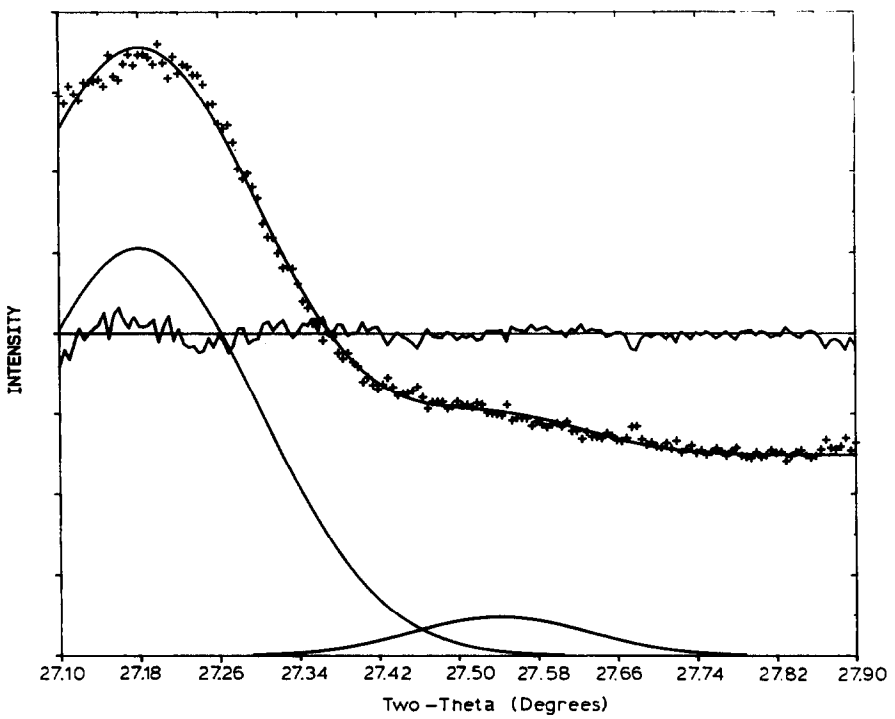

Fig. 6. Fit of α-prazosin peak obtained from the X-ray diffraction pattern of a binary mixture of α- and δ-prazosin; weight fraction of α-prazosin, 1%.

fraction in the binary mixture of α- and δ-prazosin. The calibration curve was formed using a simple third-order polynomial fitting. The least-square fitting was carried out with an algorithm written to the MS-DOS version of the MathCAD v.2.5 mathematical microcomputer program (MathSoft, Inc., U.S.A.). The zero-order term was excluded from the interpolation function in order to ensure that the function would go through the origin. The final fitting function had the form

$$y(x) = 945x + 13.24x^2 + 2.061x^3,$$

where $y(x)$ represents the normalized integrated peak area of α-prazosin as a function of its weight fraction in the binary mixture of α- and δ-prazosin.

Results and Discussion

X-ray diffraction patterns of α-prazosin and δ-prazosin are presented in Fig. 1. The diffraction patterns differ clearly from each other. However, it is not easy to find a separate peak of α-prazosin for the quantitative analysis which is sufficiently high and does not overlap with any peak of δ-prazosin. The best choice for quantification is the peak at 27.5°. This is the highest peak of α-prazosin and shows only minor overlapping with the peak of δ-prazosin. This is seen more clearly in Fig. 2, were 5 and 0.8° strips of the original patterns are plotted.

For the determination of the zero background level in a statistically smooth enough manner, the mathematical fit of the 2Θ strip from 27.1 to 27.9° was performed. On the basis of the Gaussian fit shown in Fig. 3, the background level does

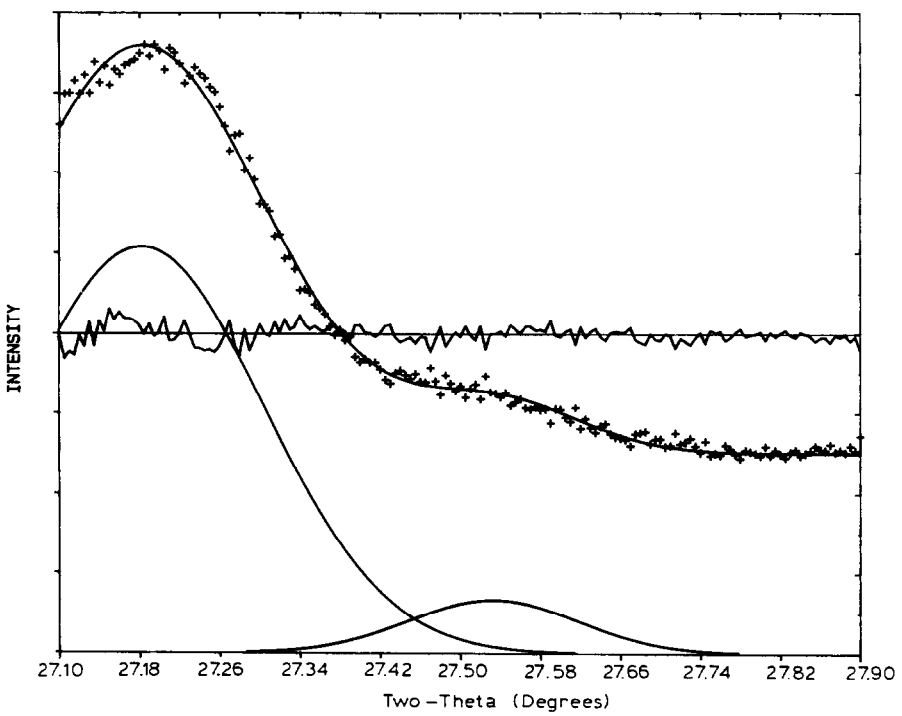

Fig. 7. Fit of α-prazosin peak obtained from the X-ray diffraction pattern of a binary mixture of α- and δ-prazosin; weight fraction of α-prazosin, 2%.

not match satisfactorily with the single line fit. The difference functions, fitted minus measured data, have systematically negative values between 27.4 and 27.6°. The correct background level was obtained by the fitting of two Gaussian functions as demonstrated in Fig. 4.

The Gaussian fits of the diffraction profiles measured from the samples of the binary mixtures of α- and δ-prazosin are presented in Figs 5–9. The plots of the difference functions seen in the figures are clear indications that the fits were satisfactorily performed. The values of the so called R factors of the fits determined as

$$R = \sum |S_o - S_c| : \sum S_o$$

where S_o and S_c represent the observed and calculated values, respectively, were in all cases below 0.03 which confirmed the quality of the fitted data.

The increase in peak area as a function of α-prazosin content in δ-prazosin is clearly evident in Figs 5–9. The integrated peak areas with and without background subtraction shown in Fig. 3 are listed in Table 1. The error estimates given in Table 1 are also part of the output from the fitting procedure and are another indication of the quality of the fit.

The calibration curve obtained on the basis of the normalized peak areas presented in Table 1 is depicted in Fig. 10. Fig. 10 clearly shows that the fit of the third-order polynomial function worked well; it is nicely continuous without any sharp changes.

On the basis of the results presented here, it can be concluded that the X-ray powder diffraction method is a very powerful technique in revealing crystalline impurities in crystalline binary powder mixtures. In this special case, where internal calibration standards and a detailed profile fitting method were used, the sensitivity of the method was as accurate as 0.5%. By use of the present analysis procedure, we are confident in stating that it is generally possible to achieve

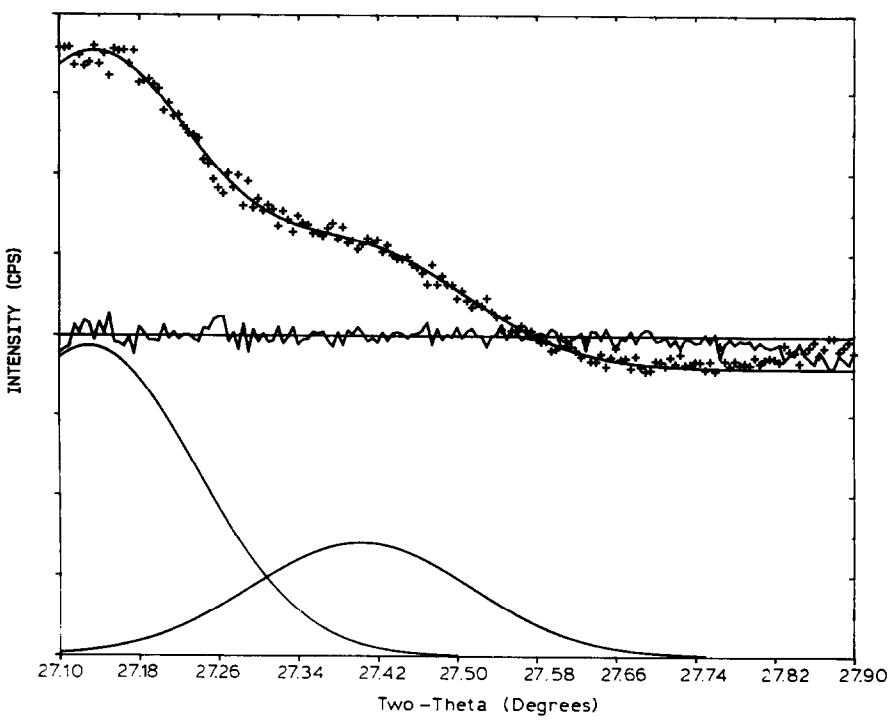

Fig. 8. Fit of α-prazosin peak obtained from the X-ray diffraction pattern of a binary mixture of α- and δ-prazosin; weight fraction of α-prazosin, 5%.

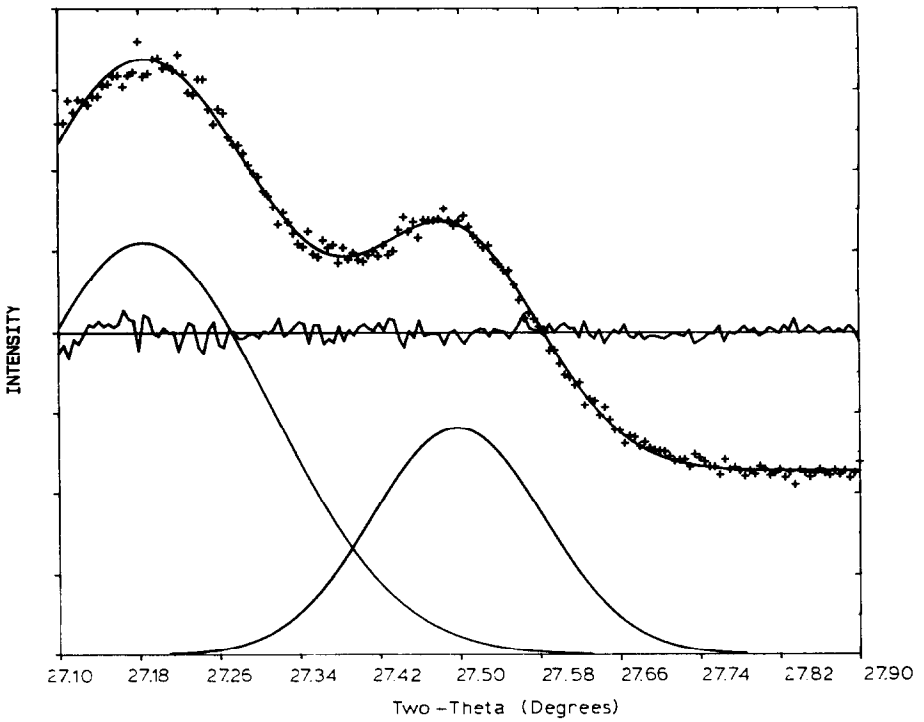

Fig. 9. Fit of α-prazosin peak obtained from the X-ray diffraction pattern of a binary mixture of α- and δ-prazosin; weight fraction of α-prazosin, 10%.

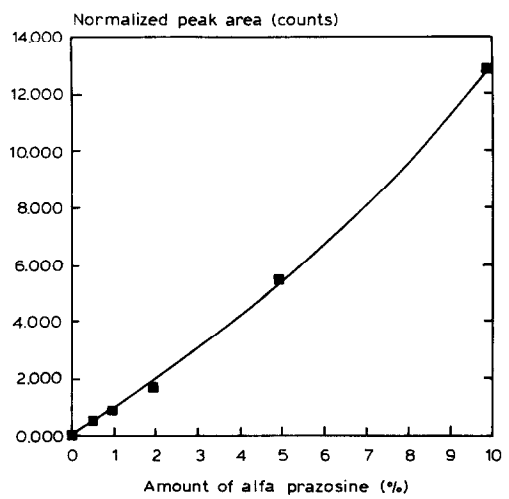

Fig. 10. Weight fraction of α-prazosin as a function of the normalized peak area of α-prazosin obtained from the diffraction pattern of a binary mixture of α- and δ-prazosin.

sensitivity equal to that reported here in cases where different crystalline modifications existing as a powder mixture are to be revealed.

TABLE 1

Integrated areas of the diffraction peaks of α-prazosin having different weight fractions measured from the diffraction profiles obtained from a binary mixture of α- and δ-prazosin hydrochloride

Weight fraction of α-prazosin	Integrated peak area	Error in peak area	Normalized peak area
0	1325	159	0
0.5	1885	288	560
1.0	2205	205	880
2.0	2930	214	1605
5.0	6834	570	5509
10	14123	258	12798

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