international
journal of
pharmaceutics

International Journal of Pharmaceutics 127 (1996) 109–112

Note

Calculated powder patterns of (R,S)-propanolol hydrochloride - a comment

William B. Gleason

Department of Laboratory Medicine and Pathology, Biomedical Engineering Center, Box 107 UMHC, University of Minnesota, Minneapolis MN 55455 USA

Received 15 September 1994; revised 21 December 1994; accepted 6 July 1995

Abstract

In contrast to a recent report by Roberts and Rowe [*International Journal of Pharmaceutics* 109 (1994) 83-87], no significant differences are found in X-ray powder patterns generated from the crystal structure description in space group $P2_1/c$ of Cotrait and Dangoumau [*C. R. Acad Sci. Ser. C.*, 272 (1971) 2057-2060] and the description in $P2_1/n$ by Ammon *et al.* [*Acta Crystallographica* B33 (1977) 21-29].

X-ray powder diffraction is a powerful technique for characterizing pharmaceutical solids. If a single crystal X-ray structural study has been carried out for a compound, then it is possible to calculate a powder pattern from the single crystal structural data and to determine whether that crystal structure is representative of the bulk sample. An experimental X-ray powder pattern can be obtained for the bulk sample and compared with a powder pattern calculated using data from the single crystal X-ray structure. Gross discrepancies indicate that the bulk sample is not well represented by the single crystal structure determination. One possible reason for such a discrepancy, of great current interest in solid-state pharmaceutics, is that the single crystal structure was determined for one polymorph of a compound while the bulk sample is, in fact, composed of a different polymorph. Lesser discrepancies may be due to contamination of the bulk sample by a different compound, or by mixtures of polymorphic forms in the bulk. Even when powder diffraction 2-theta values match calculated values well, it is still common that the experimental intensities and calculated intensities differ due to the well-known phenomenon of preferred orientation.

A recent report in this journal by Roberts and Rowe, 1994 on the powder X-ray diffraction of (R,S)-propanolol hydrochloride described an experimental powder pattern as well as two calculated powder patterns from single crystal X-ray structure determinations by Ammon et al., 1977 and by Cotrait and Dangoumau, 1971. To quote from the paper by Roberts and Rowe, 1994: "However, when two sets of data appear for (R,S)-propanolol hydrochloride (Cotrait and

SSDI 0378-5173(95)04215-V

Dangoumau, 1971; Ammon et al., 1977) the question arises as to which set is correct and representative of the powder generally used in pharmaceutical processing. Rather than perform a third study involving single-crystal X-ray diffraction, a confirmatory investigation has been undertaken using powder X-ray diffraction from a batch of bulk drug." It thus appears that Roberts and Rowe, 1994 believe the two previous sets of data describe different structures. They later state: "The data from this work compare very well with those of Ammon et al., 1977 and add to their claims that the space group is $P2_1/n$."

In fact, both sets of data are correct. They are the same structure, one described as $P2_1/c$ (Cotrait and Dangoumau, 1971) and one as $P2_1/n$ (Ammon et al., 1977). A slightly better refinement of the $P2_1/c$ structure was also made by Barrans et al., 1973. As Ammon et al., 1977 summarized the situation: "Our structure for propanolol.HCl is virtually identical to that reported by BCD [Barrans et al., 1973] with the exception of the previously indicated hydroxyl disorder; the largest differences between the two sets of fractional coordinates are of the order of 3 σ." This hydroxyl disorder does not suggest a real difference in the two studies but rather that Ammon et al., 1977 used a more sophisticated model for their analysis.

If both structures are the same then powder patterns calculated from both data sets must be the same. Figure 2 of the paper by Roberts and Rowe, 1994 compares their experimentally determined X-ray powder pattern with powder patterns generated from the Cotrait and Dangoumau, 1971 structure and from Ammon et al., 1977. Surprisingly, the calculated powder patterns are quite different. Roberts and Rowe, 1994 state that the powder pattern calculated for the Ammon et al., 1977 data is in better agreement with the experimental data than the pattern generated from the data of Cotrait and Dangoumau, 1971. They conclude: 'This provides further confirmatory evidence for the assignment of crystal dimensions and symmetry by Ammon et al., 1977.'

I have calculated powder patterns using the TEXSAN crystallographic software package (Molecular Structure Corporation, 1989) for both data sets. As can be seen in Fig. 1, the calculated powder patterns are extremely similar - the only slight differences being due to experimental error in lattice constants and the treatment of a disordered hydroxyl group which was better done by the later workers. The general shapes of both calculated patterns bear a striking resemblance to Figure 1 of Roberts and Rowe, 1994.

A quantitative comparison of the experimental powder pattern and my calculations is given in Table 1. 2-Theta and intensity values are generally in excellent agreement between the two generated powder patterns. A comparison of these patterns with the experimental values reveals some discrepancies. Intensity differences between diffraction lines with similar values of 2-theta may be ascribed to preferred orientation effects. The experimental samples may be contaminated with impurities or another polymorphic form. It should be noted that six experimentally determined lines; three of which were marked weak and three of which were described as 'Uncertain peak, not used in subsequent analysis,' were omitted during peak fitting procedures.

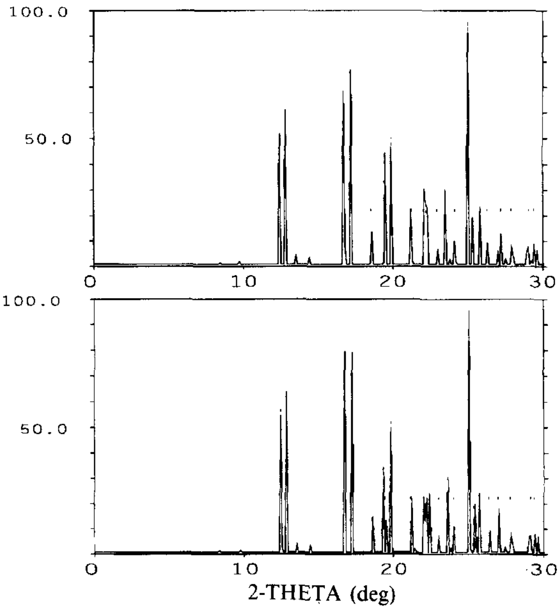

Fig. 1. Comparison between the calculated powder patterns from the crystal data of Cotrait and Dangoumau (1971) [upper] and Ammon et al. (1977) [lower].

Table 1
Comparision of experimental and calculated powder patterns for (R/S)-propanolol hydrochloride

Experimental data of Roberts and Rowe (1994)		Calculated from Ammon et al. (1977)		Calculated from Cotrait Dangoumau (1971)	
2-Theta	Intensity (normalized value)	2-Theta	Intensity	2-Theta	Intensity
8.317	17.889 (32.9)	8.31	0.7	8.38	0.6
9.736	12.507 (22.9)	9.70	0.8	9.70	1.1
12.471	42.396 (77.9)	12.45	56.8	12.42	52.6
12.777	35.988 (66.1)	12.78	34.7	12.82	29.8
		12.79	31.8	12.84	34.3
13.555[a]	1.317 (2.5)				
14.466[a]	0.825 (1.5)				
16.664	60.670 (111.5)	16.67	8.2	16.68	35.9
		16.68	37.6	16.70	36.4
		16.69	37.1	16.81	6.7
17.150	52.883 (97.2)	17.16	82.6	17.21	80.9
18.576	13.348 (24.5)	18.57	14.2	18.55	13.6
19.140[a]	8.775 (16.1)				
19.191	22.096 (40.6)				
19.324[a]	5.697 (10.5)	19.31	34.1		
19.484	28.196 (51.8)	19.46	13.4	19.46	34.0
				19.47	12.7
19.523[a]	9.483 (17.4)				
19.522[a]	0.275 (0.5)				
19.818	44.575 (81.9)	19.84	52.1	19.92	51.0
21.188	44.153 (81.2)	21.19	13.0	21.21	10.0
		21.20	9.3	21.24	12.4
22.000	22.710 (41.7)	22.04	5.8	22.07	10.3
		22.06	30.4	22.09	21.4
22.336	13.509 (24.8)	22.25	22.2	22.23	22.3
		22.40	24.1	22.30	23.7
23.046	4.397 (8.1)	23.04	5.8	22.96	5.8
23.602	23.081 (42.4)	23.59	30.4	23.49	30.7
23.688	8.417 (15.5)				
23.749	3.940 (7.2)	23.78	1.5	23.80	1.8
24.022	6.761 (12.4)	24.02	9.5	24.14	9.7
25.044	54.400 (100)	25.05	100.0	24.98	100.0
25.356	7.013 (12.9)	25.37	19.0	25.34	18.8
25.709	8.400 (15.4)	25.72	12.8	25.81	11.0
		25.74	11.8	25.85	13.2

[a] not used in analysis of Roberts and Rowe (1994)

In summary, a careful reading of the paper by Roberts and Rowe, 1994 is somewhat confusing because it appears from various statements in the paper that they believe the description of the structure in $P2_1/c$ is incorrect, the description in $P2_1/n$ is correct, and that this has been confirmed by their experimental X-ray powder pattern. Curiously, however, they also state: 'It is interesting to note that Ammon et al., 1977 showed that if an n to c unit cell transformation is carried out, this results in lattice constants of a = 14.005, b = 8.285, c = 18.243 and β = 130.59° [misprinted as 13.059], showing equivalency to the data of Cotrait and Dangoumau, 1971.' Of course, if these actually are equivalent then the calculated powder patterns must also be the same.

Acknowledgements

I thank Professors Doyle Britton and David Grant for their helpful suggestions.

References

Ammon, H.L., Howe, D.B., Erhardt, W.D., Balsamo, A., Macchia, B., Macchia, F. and Keefe, W.B., The crystal structures of dicholoroisoproterenol, propanolol and propanolol hydrochloride. *Acta Crystallogr.*, B33 (1977) 21-29.

Barrans, Y., Cotrait, M. and Dangoumau, J., Conformations cristallines d'adrenolytiques β-bloquants: propanolol et alprenolol. *Acta Crystallogr.*, B29 (1973) 1264-1272.

Cotrait, M. and Dangoumau, J., Structure cristalline du chlorhydrate de propanolol. *C. R. Acad. Sci. Ser. C.*, 272 (1971) 2057-2060.

Molecular Structure Corporation, *TEXSAN Structure Analysis Software*, MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA

Roberts, R.J. and Rowe, R.C., The unit cell dimensions of (R,S)-propanolol hydrochloride - A confirmatory study using data from powder X-ray diffraction. *Int. J. Pharm.*, 109 (1994) 83-87.