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Note

The unit cell dimensions of (*R*,*S*)-propranolol hydrochloride – A confirmatory study using data from powder X-ray diffraction

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Abstract

Powder X-ray diffraction using the new generation of laboratory based instruments has confirmed the assignment of the unit cell dimensions of $a = 14.027$ Å, $b = 8.277$ Å, $c = 13.983$ Å, $\beta = 98.843°$ and space group $P2_1/n$ for (*R*,*S*)-propranolol hydrochloride, previously defined by single-crystal X-ray diffraction by Ammon et al. (*Acta Crystallogr.*, B33 (1977) 21–29).

Key words: Powder X-ray diffraction; Unit cell dimensions; (*R*,*S*)-Propranolol hydrochloride

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A crystalline solid comprises of a rigid lattice of molecules, the locations of which are characteristic of the substance defining its physicochemical properties. The fractional coordinates, lattice dimensions and symmetry of the crystal are generally determined from single-crystal X-ray diffraction using specially grown large crystals. However, when two sets of data appear for the same material as they have done for (*R*,*S*)-propranolol hydrochloride (Cotrait and 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.

A sample of milled (*R*,*S*)-propranolol hydrochloride BP (Mol. Wt = 295.8) and a true density of 1.22 g cm^{-3} was obtained from ZENECA Pharmaceuticals.

Powder X-ray diffraction patterns were obtained using a Siemens D5000 X-ray diffractometer. The sample was pre-ground in a mortar and pestle and mixed with about 5% α-quartz to correct for sample displacement during measurement. The samples were packed into polystyrene mounts and measured without spinning. The V6 variable slit was used with additional detector slits of 0.6 and 0.05 mm and a step size of 0.01° 2θ over a scan of 2–28° 2θ The generator was operated at 40 kV, 40 mA, with a copper target and wavelength of the beam of 1.5406 Å ($K\alpha_1$)

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and 1.5443 Å (Kα_2). The step time for illumination of the sample was 60 s, giving a total run time of approx. 45 h.

The first part of the procedure is to correct for the displacement of the powder bed by using the program DIFFRAC AT (Siemens AG, Karlsruhe, Germany) by moving the pattern along the 2θ axis based on the known position of a peak for α-quartz (26.650 – from JPDS database) using a cosine function. The powder pattern generated after this procedure can be seen in Fig. 1.

An accurate measurement of the first 30 peak positions (two peaks were not measured since they belong to α-quartz) was then determined using the program FIT (Siemens AG, Karlsruhe, Germany), which is a profile fitting routine using various mathematical functions (e.g., possible profile functions to choose were Gaussian, Lorentz, Pseudo Voigt, Pearson 7 or Split Pearson 7, Voigt1 and Voigt2) to fit an individual peak. The choice of best fit for each peak was made by examining the ability of each of the functions to give the lowest reliability value (this gives the goodness of fit and is related to the differences between calculated and observed intensities for the fitted data points). The peak positions determined by this procedure are given in Table 1.

Once the peak positions (2θ) had been accurately determined the 21 lines in Table 1 were indexed using the program TREOR (this is a trial and error powder indexing program for all symmetries, which searches for solutions by varying the Miller indices – Werner et al. (1985), version 4). Initially, the program was tested for higher symmetry crystal classes but this resulted in no solutions. The control parameters of MONO = 150° (maximum beta angle allowed in monoclinic cell, as based on the beta angle of Cotrait and Dangoumau (1971)) and VOL = 2000 Å (based on calculation of volume from true density, Mol. Wt and $Z = 4$, e.g., 1616.4 Å) were subsequently tested and found to give several solutions (Table 2) with various figures of merit, M_{20} (this is an estimation of the reliability of the indexed unit cell, if $M_{20} < 6$ then the given cell is in doubt. When $M_{20} < 10$ (with the number of unindexed lines not more than 2) then this guarantees that the indexing is substantially correct (De Wolff, 1968)). The best solution is shown at the top of

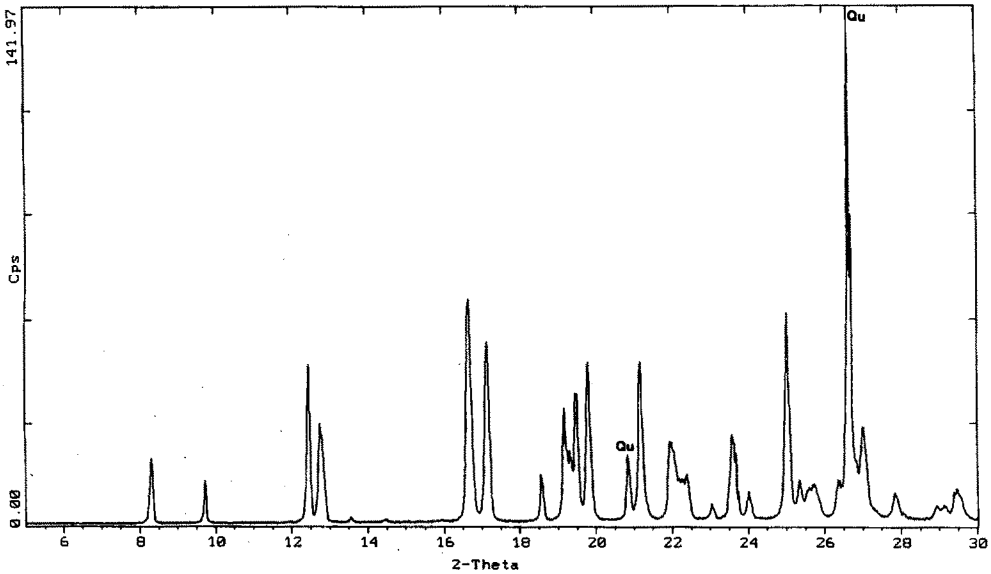

Fig. 1. Corrected powder pattern for (*R,S*)-propranolol hydrochloride, with peaks for the internal standard, α-quartz, indicated by Qu.

Table 2, with a monoclinic cell with two unindexed lines – the second line of the doublet at 22.336 and the second line of the triplet at 23.688. Since both of these lines are not distinct features (see Fig. 1), it was decided to accept this as a suitable solution for the unit cell. It is interesting to note that the unit cell solution with the third highest figure of merit gives the same dimensions but only one unindexed line.

A comparison between data from both powder X-ray diffraction and literature single-crystal X-ray diffraction, for the determination of unit cell dimensions, is given in Table 3. 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 $P2_1/n$. They suggested that the choice of $P2_1/n$ was as a result of $\beta = 98.8°$. We agree with this assignment based on the systematic absences of certain reflections. 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 $\beta = 13.059°$, showing equivalency to the data of Cotrait and Dangoumau (1971) (see Table 3).

Finally, simulated powder X-ray diffraction patterns were generated from known crystal structure data (e.g., Cotrait and Dangoumau (1971) and Ammon et al. (1977)) using the program XQPA91 (Weiss et al., 1983) for compari-

Table 1
Peak positions, d spacing, peak height, full width height maximum (FWHM) and profile function used to fit the peaks using the program FIT (Siemens AG, Karlsruhe, Germany)

Number of peaks	Position (° 2θ)	d (Å)	Height (Cps)	FWHM	Function used to fit peak
1	8.317	10.62219	17.889	0.0978	SPLIT P7
1	9.736	9.07691	12.507	0.0705	PS.VOIGT
1	12.471	7.09203	42.396	0.0922	SPLIT P7
1	12.777	6.92305	35.988	0.2217	SPLIT P7
1 [b]	13.555	6.52717	1.317	0.0937	PS.VOIGT
1 [b]	14.466	6.11808	0.825	0.1457	PEARSON7
1	16.664	5.31580	60.670	0.1531	SPLIT P7
1	17.150	5.16612	52.883	0.1491	PS.VOIGT
1	18.576	4.77263	13.348	0.1045	PS.VOIGT
1 [c]	19.140	4.63334	8.775	0.0211	PS.VOIGT [a]
2	19.191	4.62101	22.096	0.1085	
3 [c]	19.324	4.58971	5.697	0.0910	
4	19.484	4.55236	28.196	0.1303	
5 [c]	19.523	4.54336	9.483	0.0376	
6 [b]	19.522	4.54356	0.275	0.0073	
1	19.818	4.47640	44.575	0.1342	PS.VOIGT
1	21.188	4.18982	44.153	0.1275	PS.VOIGT
1	22.000	4.03699	22.710	0.2382	PS.VOIGT
2	22.336	3.97702	13.509	0.3539	
1	23.046	3.85613	4.397	0.1509	PS.VOIGT
1	23.602	3.76650	23.081	0.1679	PS.VOIGT
2	23.688	3.75298	8.417	0.0229	
3	23.749	3.74352	3.940	0.0201	
1	24.022	3.70155	6.761	0.1429	PS.VOIGT
1	25.044	3.55276	54.400	0.1333	PEARSON7
1	25.356	3.50977	7.013	0.1122	SPLIT P7
1	25.709	3.46235	8.400	0.3780	PEARSON7

[a] Difficult peak to resolve only two strongest peaks used in analysis, because of the uncertainty in the other peaks.
[b] Weak peak which was not used in subsequent analysis.
[c] Uncertain peak which was not used in subsequent analysis.
SPLIT P7, Split Pearson 7; PS.VOIGT, Pseudo Voigt; PEARSON7, Pearson 7.

Table 2
List of unit cells indexed using TREOR in order of increasing figure of merit

Figure of merit	*a* (Å)	*b* (Å)	*c* (Å)	*α* (deg)	*β* (deg)	*γ* (deg)	Number of unindexed lines
19	14.027	8.277	13.983	90	98.843	90	2
14	18.423	5.364	10.496	90	90	90	9
13	14.025	8.286	13.968	90	98.823	90	1
13	21.137	21.137	5.368	90	90	120	11
12	19.001	10.664	8.372	90	106.556	90	4
12	9.424	21.314	8.178	90	105.055	90	4
11	10.681	21.288	9.980	90	124.492	90	4
11	10.681	21.288	9.641	90	121.447	90	4
11	10.707	21.257	8.851	90	121.567	90	5
10	9.683	21.257	8.851	90	109.586	90	5
9	10.858	18.208	9.650	90	98.391	90	3
7	9.934	21.308	9.289	90	112.818	90	2
6	22.044	4.978	18.297	90	110.100	90	3

Table 3
Comparison of unit cell dimensions from this work with literature data

Technique	*a* (Å)	*b* (Å)	*c* (Å)	*β* (deg)	Reference
Powder	14.027	8.277	13.983	98.843	This work
Single crystal	14.017	8.285	14.005	98.76	Ammon et al. (1977)
Single crystal	14.005	8.285	18.285	130.59	Cotrait and Dangoumau (1971)

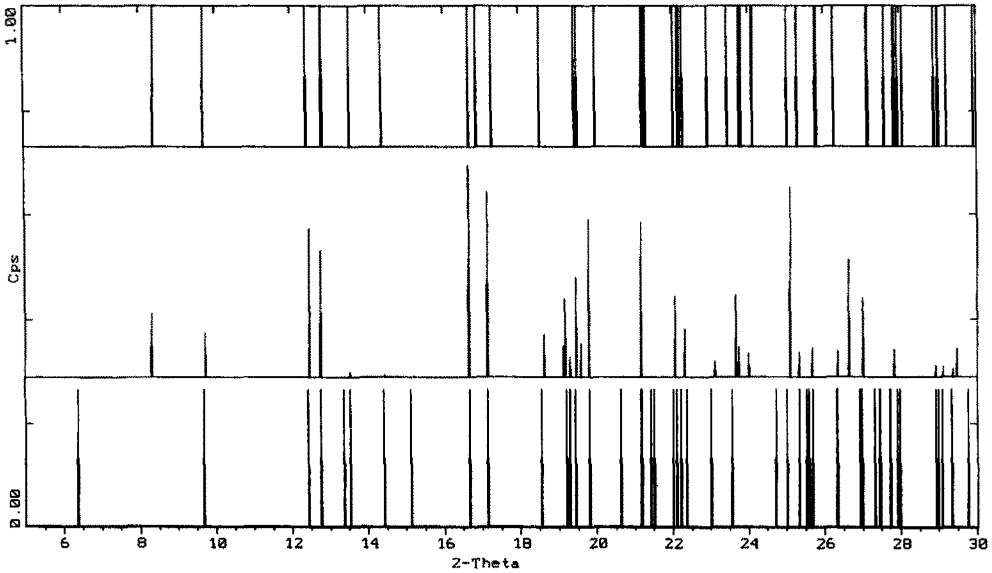

Fig. 2. Comparison between the measured powder pattern (centre), and generated patterns from crystal data of Ammon et al. (1977) (lower) and Cotrait and Dangoumau (1971) (upper).

son with the measured powder pattern (Fig. 2). It can be seen that the best agreement occurs when crystal data from Ammon et al. (1977) are compared, despite the appearance of a peak at 6.38° 2θ which does not appear in the measured powder pattern. Although there are a number of low angle peaks which are in agreement with the generated pattern from Cotrait and Dangoumau (1971), the number of common peaks is lower than that generated from the crystal data from Ammon et al. (1977). This provides further confirmatory evidence for the assignment of crystal dimensions and symmetry by Ammon et al. (1977).

In conclusion, it can be seen that the data of milled (*R,S*)-propranolol hydrochloride as used in tabletting determined using powder X-ray diffraction are representative of the single-crystal data generated by Ammon et al. (1977). An important consequence of this work is the positional accuracy obtained using the new generation of laboratory-based powder X-ray difractometers ($\pm 0.001°\ 2\theta$), allowing accurate indexing of crystal cell dimensions with extremely good figures of merit. This obviates the need to use synchrotron X-rays to generate accurate powder patterns to enable definition of lattice parameters (as recently determined for cimetidine (Cernik et al., 1991)).

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