X-ray Characterization of 12 Vasodilators in Current Use

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X-ray diffraction data have been obtained for 12 vasodilators in current use by the powder diffractometer technique. They include isoxsuprine HCl, perhexiline maleate, xanthinol nicotinate, suloctidil, pentoxyfylline, prenylamine lactate, nylidrin HCl (buphenine HCl), nifedipine, nicametate citrate, hexobendine, cyclandelate, and bamethan sulfate. The results, obtained by using the McCreery and Byström−Asklund methods of sample loading, were averaged and tabulated in terms of the lattice spacings and the relative line intensities. The method is valuable in the identification and characterization of pharmaceutical compounds from the possible polymorphic behavior of the same drug substances.

Introduction

Hannawalt and Rim (*1*) introduced the powder diffraction technique for identifying polycrystalline materials on the basis of the values of *d*1, the interplanar spacing, and I/I_0, the relative intensities of lines. This technique has been widely used in pharmaceutics for identification of drugs in current use (*2*, *3*) or in novel pharmaceutical compounds, particularly in characterization of the possible polymorphic behavior of a drug substance, because it is well-known that the improper selection of a polymorph or any polymorphic change in the dosage form can adversely influence the suspendibility, rheology, bioavailability, and stability of a formulation. Although single-crystal X-ray diffraction is one of the best methods for the characterization of polymorphs, there are often inherent difficulties to produce crystals of sufficiently high crystallographic quantity, especially for organic compounds.

Powder X-ray diffractometry has been used recently for the solid-state characterization of erythromycin A dihydrate (*4*), anhydrous theophylline (*5*), thymitaq (*6*), fosinopril sodium (*7*), imipenem (*8*), and dehydroepiandrosterone (*9*) and for monitoring the kinetics of the solid-state reaction between the enantiomers of pseudoephedrine (*10*).

Experimental Section

Diffraction patterns for 12 vadodilators were recorded by the powder diffraction technique. Samples bought from Sigma Chemical Co. included isoxsuprine hydrochloride ($C_{18}H_{23}NO_3$,HCl), perhexiline maleate ($C_{19}H_{35}N$, $C_4H_4O_4$), xanthinol nicotinate ($C_{13}H_{21}N_5O_4$,$C_6H_5NO_2$), suloctidil ($C_{20}H_{35}NOS$), pentoxyfylline/oxpentifylline ($C_{13}H_{18}N_4O_3$), nylidrin hydrochloride/buphenine hydrochloride ($C_{19}H_{25}NO_2$, HCl), nifedipine ($C_{17}H_{18}N_2O_6$), nicametate citrate ($C_{12}H_{18}N_2O_2$, $C_6H_8O_7$), cyclandelate ($C_{17}H_{24}O_3$), and bamethan sulfate ($(C_{12}H_{19}NO_2)_2$, H_2SO_4. The rest of the compounds, prenylamine lactate ($C_{24}H_{27}N$, $C_3H_6O_3$) and hexobendine ($C_{30}H_{44}N_2O_{10}$), were kindly donated by Hoechst Hellas AG, Athens,Greece, and Minerva, Athens, Greece, respectively. The molecular structures and other analytical characteristics of the compounds are described extensively in the literature (*11*, *12*). The purity of most pharmaceutical compounds is not less than 98% (*13*).

The X-ray powder diffractometer patterns were recorded by mounting ≈1 g of ground sample in a window of an aluminum specimen holder and then exposing it to the X-ray beams (Cu Kα radiation) for about 40 min. It was essential, for the most satisfactory results, that the number

Table 1. Values of Interplanar Spacings and Relative Intensities of Lines[a]

d/Å	I/I_0	*d*/Å	I/I_0	*d*/Å	I/I_0
Isoxsuprine Hydrochloride					
11.63	3	3.769	17 sh	2.805	2
10.05	**75**	**3.723**	**48**	2.747	2 b
9.72	45 sh	3.678	45	2.706	4
7.44	7	3.590	7	2.607	1
7.03	3	3.466	16	2.578	1
5.95	18 sh	3.440	14	2.522	1
5.83	**100**	3.376	6	2.488	1
5.57	14	3.326	3	2.455	1
5.37	26	3.255	33	2.430	1
5.25	11	3.187	3 b	2.332	3 b
4.93	26 sh	3.110	2	2.287	3 b
4.87	44	3.028	3		
4.77	19	2.979	4		
4.19	12	2.940	4		
4.08	13	2.903	8		
3.969	14	2.885	4 sh		
3.883	26	2.831	2		
Perhexiline Maleate					
13.29	3 b	4.02	11		
9.80	**100**	**3.834**	**65**		
9.12	12	3.754	24		
8.59	9	3.663	19 sh		
5.96	11	3.604	51		
5.70	26	3.562	6 sh		
5.19	32 sh	3.440	3		
5.04	**86**	3.302	5		
4.98	38 sh	3.267	3		
4.93	18 sh	3.209	7		
4.75	52	3.048	3 b		
4.53	53	2.931	3		
4.48	31 sh	2.867	3		
4.40	14 sh	2.763	4 b		
4.32	38				
4.23	11 sh				
4.15	8				

[a] The three most intense lines are in bold. sh = shoulder attached to strong line. b = broad line.

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Table 2. Values of Interplanar Spacings and Relative Intensities of Lines[a]

d/Å	I/I_0	d/Å	I/I_0	d/Å	I/I_0
		Xanthinol Nicotinate			
11.12	**75**	**3.715**	**68**	2.755	4 b
9.61	1 b	3.663	16 sh	2.683	13
8.06	**100**	3.562	12 sh	2.622	10 b
6.97	3	3.507	42 sh	2.607	8 sh
6.56	30 sh	3.486	52	2.501	8
6.51	36	3.414	11 sh	2.462	2 sh
5.99	47	3.351	40 sh	2.442	1 sh
5.83	23	3.339	50	2.404	1 b
5.35	55	3.255	15	2.368	2 b
5.16	32	3.175	16	2.338	2 b
5.01	4 sh	3.121	6	2.304	4 b
4.93	2 sh	3.033	20	2.292	1 sh
4.67	4 sh	2.979	5 sh		
4.53	49	2.940	52		
4.17	23	2.849	12		
4.00	10 sh	2.805	6		
3.917	35	2.771	5		
		Suloctidil			
10.78	32	3.900	3	2.557	3
8.27	18	3.738	33	2.501	8
7.25	**100**	3.619	12	2.455	1
6.92	2 sh	3.414	3	2.411	1
6.24	3	3.351	4 sh	2.380	1
5.61	6 sh	3.314	6	2.350	1
5.44	**84**	3.243	7	2.270	1
5.10	5 sh	3.220	5 sh	2.171	6 b
4.98	31	3.099	14	2.113	15
4.75	29	3.038	3		
4.63	18 sh	2.931	3		
4.48	75	2.885	6		
4.37	**80**	2.823	3		
4.29	32 sh	2.788	3		
4.13	12 sh	2.747	2		
4.08	17	2.706	3		
		2.614	3		

[a] The three most intense lines are in bold. sh = shoulder attached to strong line. b = broad line.

Table 3. Values of Interplanar Spacings and Relative Intensities of Lines[a]

d/Å	I/I_0	d/Å	I/I_0	d/Å	I/I_0
		Pentoxyfylline			
12.03	23 sh	3.562	3 sh	2.550	8
11.63	48	3.520	3 sh	2.321	2 sh
11.33	42	3.466	10	2.309	2
6.97	**60**	3.363	24	2.171	3 b
6.76	42	3.255	6 sh	2.146	2 b
6.51	28	3.192	52	2.113	1 b
6.03	17 sh	3.132	4 sh	2.067	1 b
5.83	**100**	3.110	3 sh		
5.64	16 sh	3.058	4		
4.46	8 sh	2.988	12		
4.33	24	2.903	2		
4.27	17 sh	2.831	4 sh		
4.08	49	2.814	6		
3.969	43	2.751	7 b		
3.883	6 sh	2.683	4		
3.770	35 sh	2.652	1		
3.693	**93**	2.600	6		
		Prenylamine Lactate			
14.26	**63**	4.44	44	2.644	5 b
9.72	7	**4.19**	**100**	2.529	3 b
8.27	2	4.06	10 sh	2.430	4 b
7.66	9	4.00	13	2.277	3 b
7.26	3 b	3.786	17		
6.71	39	3.723	24		
6.66	35 sh	3.678	21 sh		
6.15	4	3.619	11 b		
5.87	13 b	3.520	5 b		
5.79	11 b	3.453	17		
5.57	27 sh	3.339	5		
5.44	44	3.220	23		
5.25	13 sh	3.164	12		
5.07	**78**	3.069	10		
4.82	16 sh	2.940	7 b		
4.72	35	2.816	5 b		
4.53	58	2.698	5 b		

[a] The three most intense lines are in bold. sh = shoulder attached to strong line. b = broad line.

of crystallites contributing to each reflection was of the appropriate size and that the effect of the preferred orientation of the crystallites was held to a minimum, since there is a close correlation between the method of packing and the reproducibility of the patterns. In this method a

Table 4. Values of Interplanar Spacings and Relative Intensities of Lines[a]

d/Å	I/I_0	d/Å	I/I_0	d/Å	I/I_0
		Nylidrin Hydrochloride			
11.63	4	4.17	60	2.722	7 sh
10.22	**100**	4.13	20 sh	2.648	4 b
9.83	12 sh	**3.952**	**98**	2.596	2 b
9.61	28	3.818	4	2.553	5 b
8.51	3 b	3.762	12	2.445	2 b
7.76	2 b	3.693	12	2.383	2 b
6.92	5 b	3.626	11		
6.42	27	3.562	26		
6.01	9	3.370	23 b		
5.75	7	3.192	15 b		
5.63	13 sh	3.132	5 b		
5.50	18	3.079	2 b		
5.22	17	3.003	8 b		
4.98	**95**	2.936	10 b		
4.72	43	2.880	5 b		
4.54	37	2.801	7 b		
4.26	40	2.747	11 b		
		Nifedipine			
11.63	4 sh	3.969	30		
10.98	41	3.917	32		
8.51	34	3.786	1 sh		
7.56	**100**	3.633	12 sh		
6.81	8	3.612	43 b		
6.61	2 sh	3.447	24		
6.03	**43**	3.389	23 b		
5.50	29	3.302	27		
5.21	22	3.203	6 b		
4.85	9	3.148	4 sh		
4.67	15 sh	3.018	5 b		
4.53	**52**	2.945	1 b		
4.50	21 sh	2.734	4 b		
4.28	6 sh	2.505	3 b		
4.21	10 b	2.374	2 b		
4.15	8 sh				
4.06	27				

[a] The three most intense lines are in bold. sh = shoulder attached to strong line. b = broad line.

Table 5. Values of Interplanar Spacings and Relative Intensities of Lines[a]

d/Å	I/I_0	d/Å	I/I_0	d/Å	I/I_0
		Nicametate Citrate			
10.78	2	4.40	30 sh	2.637	10 b
10.16	4	4.37	32	2.585	5 b
9.61	5	4.20	16 sh	2.508	6 b
8.80	**100**	4.13	25	2.417	6 b
7.44	60	3.867	18 b	2.368	4 b
7.20	37	3.818	14 sh	2.332	3 b
6.86	31	**3.590**	**68**	2.284	2 b
6.71	31	3.527	29		
6.46	45	3.473	45		
6.19	9	3.363	18		
5.64	22	3.320	15		
5.44	**79**	3.232	8		
5.04	56	3.105	27		
4.83	30	3.038	31 b		
4.67	14 sh	2.858	6 b		
4.56	65	2.793	4 b		
4.46	29	2.698	21 b		
		Hexobendine			
13.19	5 b	4.46	60	2.805	6 b
8.76	**87**	4.37	33	2.629	6 b
8.27	1	4.25	44 b	2.550	4 b
7.90	3	4.19	36 sh	2.327	4 b
7.69	3	4.04	17 sh		
7.50	1	3.952	62 sh		
7.03	30	**3.883**	**100**		
6.92	21 sh	3.738	20		
6.64	27	3.506	55		
6.56	24 sh	3.453	50		
6.42	12	3.326	43 sh		
5.99	**70**	3.278	47 b		
5.70	62	3.197	31		
4.98	11	3.069	10 b		
4.80	20	2.979	10 b		
4.72	21	2.903	6 b		
4.58	14 sh	2.876	8 b		

[a] The three most intense lines are in bold. sh = shoulder attached to strong line. b = broad line.

sometimes noticeable source of error is the preferred orientation; therefore, the method of loading the samples necessitates careful consideration because the variation of line intensities can lead to different conclusions relative

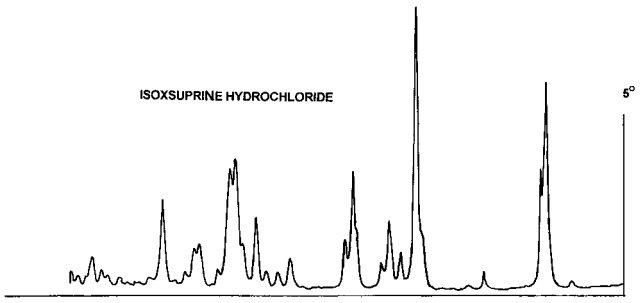

Figure 1. X-ray powder diffraction pattern of isoxsuprine hydrochloride.

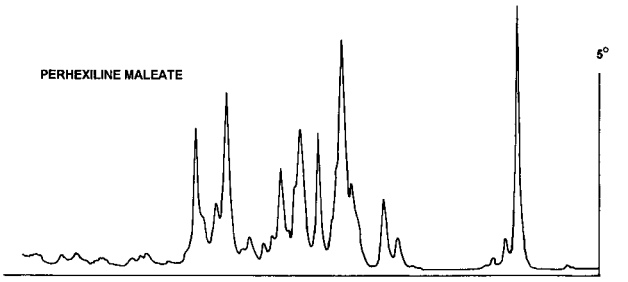

Figure 2. X-ray powder diffraction pattern of perhexiline maleate.

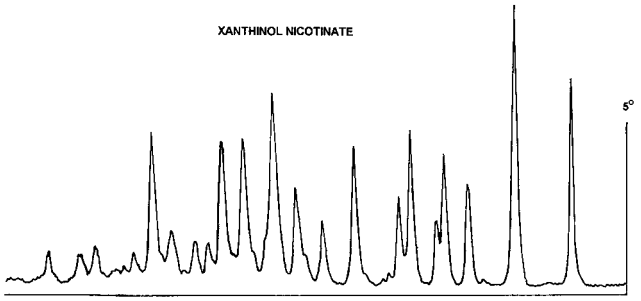

Figure 3. X-ray powder diffraction pattern of xanthinol nicotinate.

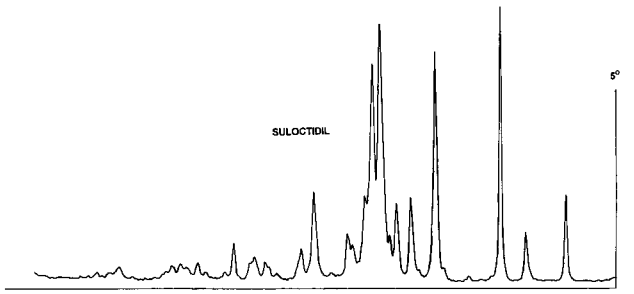

Figure 4. X-ray powder diffraction pattern of suloctidil.

to the characterization of the drug substance, its polymorphs, and solvates. The Philips diffractometer goniometer (PW 1050/25) was used in conjunction with a Xenon proportional counter (PW 1965/30) and a Philips rate meter/single-channel analyzer (PW 4620) with output to a chart recorder (PM 8000). Nickel-filtered copper radiation (Cu Kα 1.542 Å) was produced by a normal focus tube operated at 40 kV and 20 mA.

In the patterns obtained by the powder diffractometer, each centimeter was equal to 1° of 2° on the chart paper output. The lattice spacing (d, Å) was calculated using the Bragg equation $d = 1.5418/2 \sin \theta$. Samples were scanned at 20 °C over the 2θ range 5−45° at 1°/min. The relative intensities (I/I_1) were measured simply in terms of peak height (I) above background, relative to the peak height above background for the strongest line (I_1) in each pattern, taken as 100.

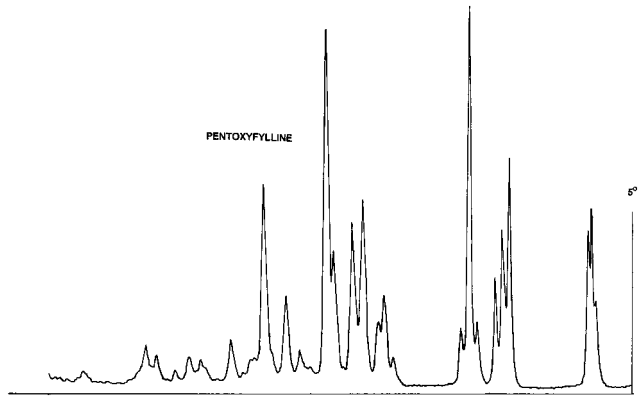

Figure 5. X-ray powder diffraction pattern of pentoxyfylline.

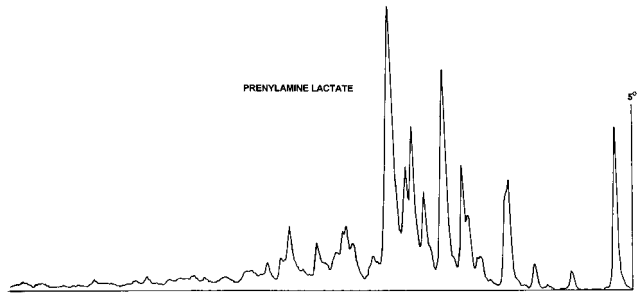

Figure 6. X-ray powder diffraction pattern of prenylamine lactate.

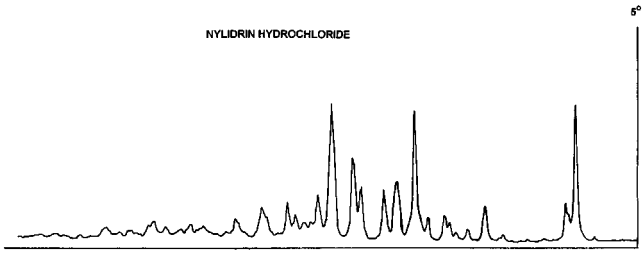

Figure 7. X-ray powder diffraction pattern of nylidrin hydrochloride (buphenine).

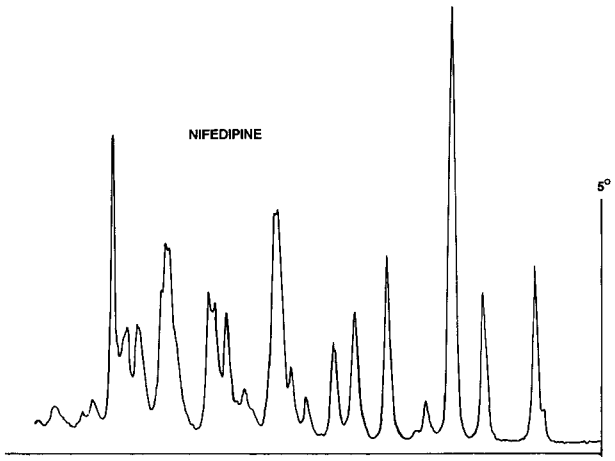

Figure 8. X-ray powder diffraction pattern of nifedipine.

The data presented in Tables 1−6 have already been submitted to the International Centre for Diffraction Data. However, in the present work additional information is provided concerning mainly variations of the line intensities in the patterns of the 12 vasodilators.

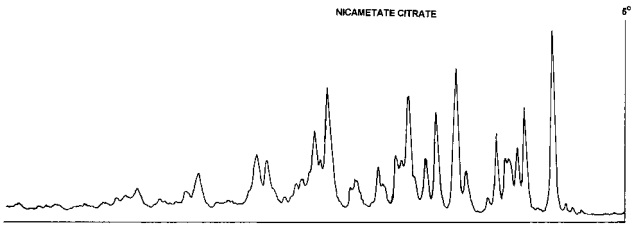

Figure 9. X-ray powder diffraction pattern of nicametate citrate.

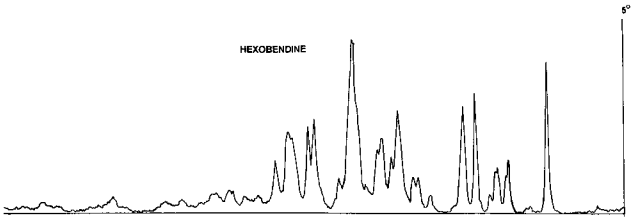

Figure 10. X-ray powder diffraction pattern of hexobendine.

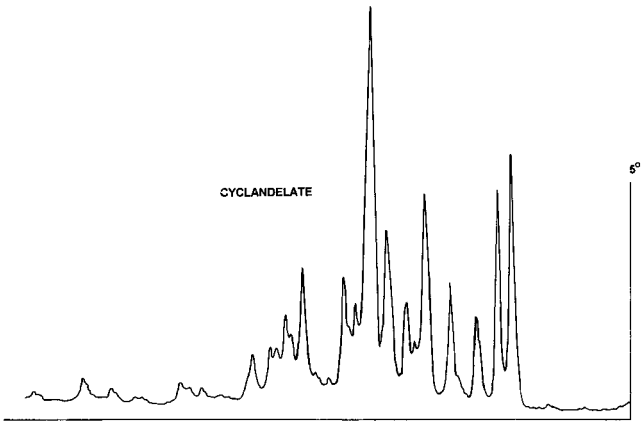

Figure 11. X-ray powder diffraction pattern of cyclandelate.

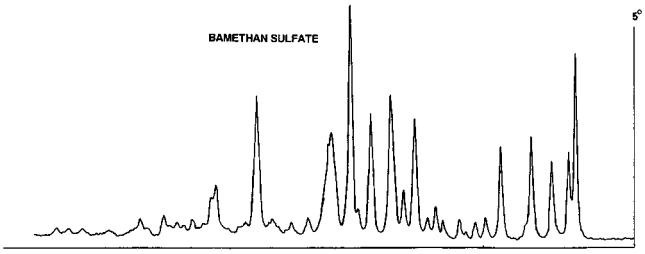

Figure 12. X-ray powder diffraction pattern of bamethan sulfate.

Results and Discussion

Tables 1 and 2 and Figures 1−12 show the data and the X-ray patterns obtained for the 12 vasodilators in terms of the lattice spacings and the relative intensities of the lines. These, which characterized the 12 vasodilators, are not described in full detail in the Powder Diffraction File. Some of them yield very characteristic patterns, whereas for others the intensity of lines can vary with the method of loading the sample. In Tables 1−6 the values of the line intensities in most cases are an average of the results obtained for a compound by repeated loadings of the two methods of preparing the crystalline material: the McCreery method, loading the powder from the back, and the Byström−Asklund method, loading the sample from the edge.

In isoxsuprine HCl the three most intense lines are observed at 5.83 Å (100), 10.05 Å (75), and 3.723 Å (*48*). Frequently, the first two lines yield a characteristic shoulder whereas the third line is rather broad and sometimes splits into a doublet. In perhexiline maleate the most intense lines appear at (9.80, 5.04, 4.75, 3.834, and 3.604) Å and vary according to the sample preparation. The maximum intensity values may change among themselves. The region in the pattern from 15° to 21° is very characteristic for the compound. Xanthinol nicotinate reveals a reproducible pattern with the three most intense lines at (8.06, 11.12, and 3.715) Å. In addition the most intense lines appear at (3.486 and 3.339) Å. The most reproducible part of the pattern is from 12° to 18° with two characteristic doublets at (5.99−5.83) Å and (5.35−5.16) Å. Suloctidil is characterized by the five most intense peaks at (10.78, 7.25, 5.44, 4.48, and 4.37) Å. In the region from 17° to 22° (d = 5.10−4.08) Å, the existing lines are recorded with variable intensities; therefore, the line at 4.37 Å is not always one of the three most intense lines in the pattern. Pentoxifylline gives a very reproducible pattern. It was observed that the pattern derived from the side-loaded method is characterized by sharp and prominent lines. In prenylamine lactate the most intense lines are observed at (14.26, 5.44, 5.07, and 4.19) Å. The doublet at (4.53 and 4.44) Å is very characteristic and splits into two peaks of different intensities. For nylidrin HCl the three most intense lines are very reproducible by using different methods of loading the sample. The region from 17° to 23° (d = 5.22−3.762) Å is very characteristic of the compound. Nifedipine is characterized by the five most intense lines at (7.56, 6.03, 5.50, 4.53, and 3.302) Å, which include the three most intense lines. The line at (7.56) Å is very reproducible whereas the others vary with the method of loading the sample. Nicametate citrate reveals a characteristic series of lines from 11.9° to 15.7° (d = 7.44−5.64) Å, which are very reproducible together with the two most intense lines at (8.80 and 5.44) Å. The third intense line can appear at (4.56 or at 3.590) Å.

Table 6. Values of Interplanar Spacings and Relative Intensities of Lines[a]

d/Å	I/I_0	d/Å	I/I_0	d/Å	I/I_0
		Cyclandelate			
11.95	1 b	3.978	34		
9.46	1 b	3.883	18 sh		
7.80	**64**	3.834	23		
7.34	**55**	3.754	15		
6.73	23	3.700	14		
6.28	8 sh	3.569	13		
6.07	31	3.401	1 b		
5.57	53	3.351	2 b		
5.40	17	3.226	4 b		
5.25	26	3.159	4 b		
4.94	43	3.099	5 b		
4.72	**100**	2.903	1 b		
4.55	25	2.763	3 b		
4.46	12 sh	2.637	5 b		
4.41	32	2.162	2 b		
4.25	7 b				
4.11	8 sh				
		Bamethan Sulfate			
10.40	**81**	4.25	12 sh	2.894	5
9.94	38	**4.15**	**100**	2.858	6
8.98	34	3.952	45 b	2.823	6 sh
8.04	45	3.917	41 sh	2.788	10
7.83	7 sh	3.739	9	2.714	4
6.94	40	3.590	7	2.675	8
6.51	9	3.480	6 sh	2.550	3 b
6.24	7	3.453	8	2.501	1
6.03	3 sh	3.427	6 sh	2.442	3 b
5.87	9	3.333	60	2.398	3 b
5.54	8	3.266	6	2.356	3 b
5.37	14	3.232	3 sh		
5.22	9	3.153	3 sh		
5.01	52	3.069	22		
4.85	21	3.038	16 sh		
4.65	**62**	2.298	4 sh		
4.37	54	2.931	7		

[a] The three most intense lines are in bold. sh = shoulder attached to strong line. b = broad line.

In hexobendine the most intense lines are at (8.76 and 5.99) Å. The third most intense line can appear either at 3.883 Å as a broad line or at 3.278 Å. For cyclandelate the three most intense lines can vary among (7.80, 7.34, 5.57, 4.72, and 3.978) Å whereas for bamethan H_2SO_4 the same lines are assigned at (10.40, 4.65, 4.15, and 4.37) Å. The compound yields sharp peaks, and the pattern from 17° to 23.8° (5.22 to 3.739) Å is very reproducible.

In conclusion, the data presented show no fundamental discrepancies in the *d* spacings. Differences in the intensities of the strongest lines in the diffraction patterns have been pointed out. Several runs of different sample loadings have shown that the results are both reproducible and reliable.

Registry Numbers of the Drug Substances (CAS Number)

isoxsuprine hydrochloride, 579-56-6; perhexiline maleate, 6724-53-4; xanthinol nicotinate, 437-74-1; suloctidil, 54063-56-8; pentoxyfylline, 6493-05-6; prenylamine lactate, 69-43-2; nylidrin hydrochloride (buphenine), 900-01-6 (replaced), 849-55-8; nifedipine, 21829-25-4; nicametate citrate, 1641-74-3; hexobendine, 54-03-5; cyclandelate, 456-59-7; bamethan sulfate, 5716-20-1.

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