X-ray Powder Diffraction Data for 12 Drugs in Current Use

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Characterization of bulk drugs has become increasingly important in the pharmaceutical industry. A multitude of analytical techniques are commonly employed for this purpose. In this work X-ray diffraction data have been obtained for 12 well-known drugs in current use by the powder diffractometer technique. They include atenolol, benactyzine hydrochloride, dicyclomine (dicycloverine) hydrochloride, dyclonine hydrochloride, dimenhydrinate, guanethidine sulfate (ismelin), halozone, metoclopramide, oxprenolol hydrochloride, oxybuprocaine (benoxinate) hydrochloride, primidone, and thiomersal (thimerosal) sodium. 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. One of the advantages of the method is that it provides additional information about the crystalline state of the active ingredients. Furthermore, the crystalline state is related to the suspendibility, rheology, bioavailability, and possible stability of pharmaceutical formulations during manufacturing process and storage time.

Introduction

X-ray powder diffractometry (XRD) is an effective technique for the identification of crystalline solid-phase drugs. The crystalline solid phase has a unique XRD pattern characterized on the basis of the values of the inteplanar spacing, d/Å, and the relative intensities of lines, I/I_1. The use of the X-ray pattern for the identification of materials was first suggested by Hanawalt and Rimm.[1] The technique is unique, since it combines specificity with a high degree of accuracy for the characterization of pharmaceuticals in solid state[2] and is an especially useful method to describe the possible polymorphic behavior of drug substances.[3] It also permits the simultaneous identification of multiple active ingredients in different pharmaceutical formulations. Despite these attributes, the method finds relatively limited applications for the evaluation of drug product quality. The technique has been used recently for identification of drugs in pharmaceutical dosage forms,[4] in the determination of α-impurities in the β-polymorph of inosine,[5] in the investigation of the solid state of fluocinolone, acetonide,[6] and candesartan cilexetil (TCV-116),[7] in the characterization of polymorphic forms and solvates of glibenclamide and paracetamol,[8−10] and in the study of the polymorphism comparison of oxytetracycline hydrochloride powders.[11]

The aim of this paper is to present the XRD patterns together with the values of the d spacing of the drugs and to point out the variations observed in different line intensities.

Experimental Section

Diffraction patterns for 12 drugs in current use were recorded by the powder diffraction technique. Samples bought from Sigma Chemical Co. included benactyzine hydrochloride ($C_{20}H_{25}NO_3$, HCl), dyclonine hydrochloride ($C_{18}H_{27}NO_2$, HCl), dimenhydrinate ($C_{17}H_{21}NO$, $C_7H_7ClN_4O_2$), halazone ($C_7H_5Cl_2NO_4S$), metoclopramide ($C_{14}H_{22}ClN_3O_2$), oxprenolol hydrochloride ($C_{15}H_{23}NO_3$, HCl), and thiomersal sodium ($C_9H_9HgNaO_2S$). Atenolol ($C_{14}H_{22}N_2O_3$), dicyclomine hydrochloride ($C_{19}H_{35}NO_2$, HCl), oxybuprocaine hydrochloride ($C_{17}H_{28}N_2O_3$, HCl), primidone ($C_{12}H_{14}N_2O_2$) (Cana AG, Athens, Greece), and guanethidine sulfate ($C_{10}H_{22}N_4$, H_2SO_4) (Ciba-Geigy) were kindly donated by the above manufacturers.

The molecular structure and other analytical characteristics of the compounds are described extensively in the literature.[12,13] The purity of most pharmaceutical compounds is not less than 98% and not more than 101%, as is clearly described in *British Pharmacopoeia*.[14]

The X-ray powder diffractometer patterns were recorded by mounting ∼1 g of ground sample in the window of an aluminum specimen holder and then exposing it to the X-ray beam (Cu Kα radiation) for about 40 min. It is essential, for the most satisfactory results, that the crystallites contributing to each reflection are of the appropriate size and that the effect of preferred orientation is reduced to a minimum, since there is a close correlation between the method of packing and the reproducibility of the patterns. The preferred orientation may sometimes introduce a noticeable error in relative intensities. Therefore, the sample loading methods must be chosen to reduce this effect to a minimum; otherwise, the variation of line intensities may lead to different conclusions relative to the characterization of the drug substances, its polymorphs, and solvates. To this end the sample preparation techniques attributed to McCreery, a back-loading method, and Byström−Asklund, a side-loading method, were used for consistency and reproducibility.[15]

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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
		Atenolol			
13.795	**100**	2.766	12		
9.191	**31**	2.670	5		
6.885	6	2.596	10		
5.502	12	2.502	13		
4.999 dbt	17	2.233	10		
4.851 dbt	17	2.072	10		
4.605	25				
4.312	**34**				
3.982	30				
3.727	29				
3.647	19				
3.613 sh	13 sh				
3.427	21				
3.368	27				
3.344 sh	18 sh				
3.061 b	10 b				
2.802 b	15 b				
		Benactyzine Hydrochloride			
15.908	52	4.095	7	2.678	10
8.801	36	3.965	17	2.645	10
7.922	10	3.847 sh	14	2.585	13
7.812 sh	8 sh	3.782	53	2.557	9
7.579	10	**3.663**	**100**	2.523	8
7.072	6	3.526	49	2.504	17
6.699	24	3.439	11	2.399	9
6.235	3	3.353	44	2.188	14
5.788	18	3.320	35	2.029	21
5.557	**71**	3.215	17		
5.290	**62**	3.184 sh	9		
4.866	6	3.106	27		
4.456	20	3.004	22		
4.404	22	2.897	10		
4.324	37	2.861	12		
4.282 sh	14	2.750	23		
4.182	4	2.705	6		

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

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
		Dicycloverine Hydrochloride			
16.636 sh	7 sh	3.972	30	2.894	4
15.800	**100**	3.927	17	2.796	5
9.073	7	3.745	13	2.720	4
7.901	5 sh	3.692 sh	6 sh	2.681	5
7.759	13	3.636	6	2.653	11
7.159	16	3.581 sh	6 sh	2.450	5
6.391 b	10 b	3.562	10	2.360	5
5.707	12	3.492 b	25 b	2.341	5
5.526	4	3.384 sh	6 sh	2.027	6
5.298	**88**	3.329	17	1.991	14
5.089	**42**	3.229 b	4 b		
4.983	12	3.182	15		
4.923 sh	4 sh	3.149	9		
4.765	17	3.108 b	6 b		
4.622	2 b	3.085	5		
4.535 b	2 b	3.009	5		
4.294	2	2.940	5		
		Dyclonine Hydrochloride			
14.288	29	3.753	2	2.346 dbt	20
10.310 sh	3	**3.586**	**41**	2.288 b	4
10.134	7	3.462	13	2.257	7
7.475	3	3.422	6	2.236	4
7.146	15	3.323	20	2.123	6
6.391	**100**	3.188 b	4	2.100	4
5.937	3	3.021	5	2.073	5
5.544	6	2.955	5	2.056	7
5.064	5	2.922	8	2.037	11
4.887 dbt	28	2.856	36	2.018	13
4.761 dbt	28	2.790	5	1.986	4
4.549 b	8	2.747 b	5		
4.374	5	2.731 b	6		
4.196 b	2	2.652	5		
4.044 dbt	**45**	2.594	7		
3.980 dbt	23	2.449 b	5		
3.885	6	2.378 dbt	30		

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

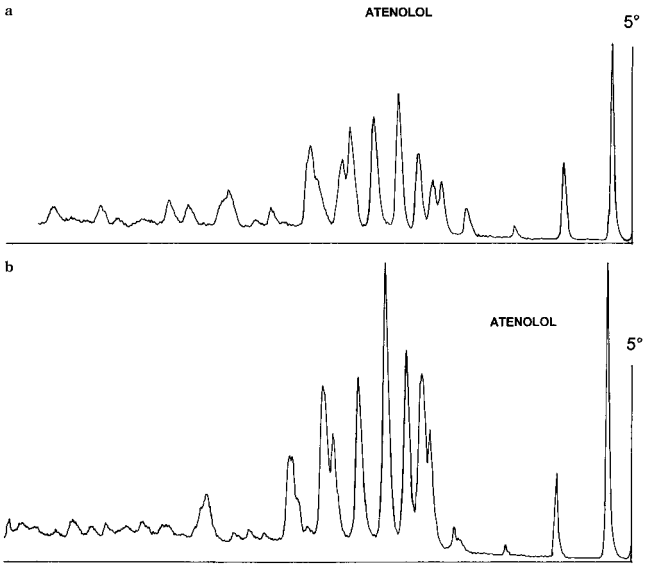

Figure 1. (a) X-ray powder diffraction pattern of atenolol (back-loading method). (b) X-ray powder diffraction pattern of atenolol (side-loading method).

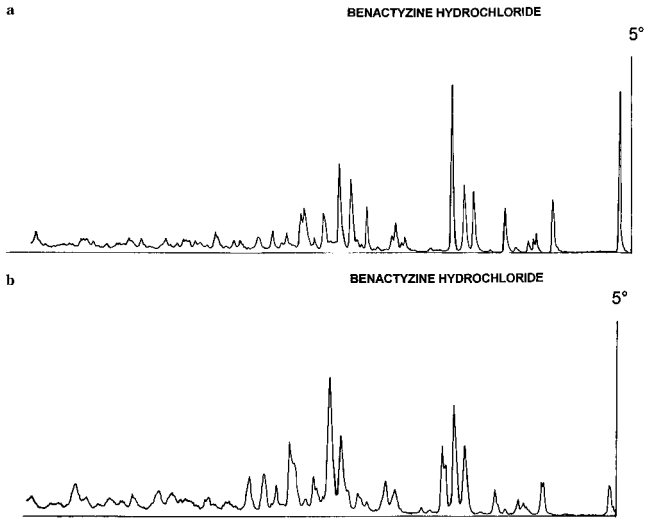

Figure 2. (a) X-ray powder diffraction pattern of benactyzine hydrochloride (back-loading method). (b) X-ray powder diffraction pattern of benactyzine hydrochloride (side-loading method).

The Philips diffractometer goniometer (PW 1050/25) was used in conjuction 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

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
		Dimenhydrinate			
13.125	2	4.062 sh	7	2.704	4
9.629 sh	4	4.001	11	2.685	4
8.445	22	3.968	9	2.656	3
8.320	**100**	3.900	10	2.586	5
6.689	12	3.691	18	2.553	9
6.574	7	3.641	5	2.518	4
6.176	4	3.475	13	2.480	3
6.005	6	3.415	4	2.441	3
5.555	2	3.330	5	2.403	3
5.369	2	3.299	18	2.389	3
5.174	4	3.237	7	2.341	2
5.074	3	3.188	9	2.312	4
4.816	5	3.140	8	2.291	3
4.674	2	3.001	4	2.196	4
4.553	**50**	2.971	5	2.180	3
4.408	40	2.845	4	2.028	6
4.163	**46**	2.770	4		
		Guanethidine Sulfate			
13.042	52	3.256 sh	15	2.171	6
6.516	**100**	3.121	28	2.085	8
6.216	2	3.065	7	2.060	5
5.972	27	3.019	4	2.032	4
5.616	10	2.983	7		
4.944	51	2.923	11		
4.668 b	2	2.828	6		
4.497	13	2.697	5		
4.341	**53**	2.651	6		
4.114	9	2.602	5		
3.772	**57**	2.524	6		
3.646	41	2.468	5		
3.609 sh	14	2.436	5		
3.560	5	2.401	15		
3.433	6	2.354	4		
3.372	10	2.233	5		
3.279	26	2.184	8		

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

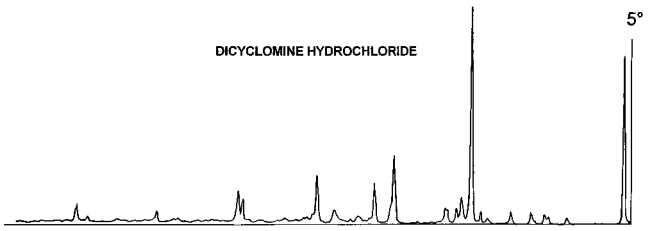

Figure 3. X-ray powder diffraction pattern of dicyclomine hydrochloride.

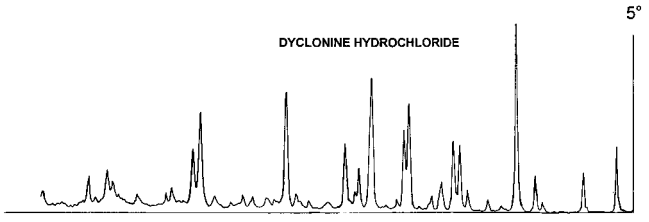

Figure 4. X-ray powder diffraction pattern of diclonine hydrochloride.

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.

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 drugs.

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
		Halazone			
9.993	31	2.987	22	2.043	7
6.551	19	2.884	4		
5.542	**100**	2.797	23		
5.208	6	2.749	18		
4.995	2	2.667	7		
4.705 b	34	2.641	12		
4.332	68	2.587	14		
3.975	67	2.568	11		
3.894 sh	11	2.502	18		
3.723	12	2.438 sh	12		
3.609	18	2.411	22		
3.411	14	2.363	9		
3.324 sh	14	2.226	19		
3.274 dbt	65	2.166	12		
3.240 dbt	**72**	2.135	8		
3.111	**90**	2.117	8		
3.059 sh	15	2.095	9		
		Metoclopramide			
13.038	**100**	3.759 b	5	2.565	4
7.849	33	3.701	30	2.519	6
7.218	2	3.605	33	2.493 b	4
6.779	14	3.535	5	2.466	4
6.613	10	**3.388**	**99**	2.403	6
6.309	29	3.341 sh	8	2.367	4
5.828	6	3.235 sh	11	2.344	7
5.438	3	3.220	46	2.309	7
5.317	1	3.126	15	2.288	8
4.912	1	3.056	7	2.200	8
4.524	2	2.901 b	14	2.180	6
4.335 sh	11	2.852	7	2.124	9
4.279	49	2.822	2	2.073	10
4.218 sh	11	2.737 b	8	2.018	9
4.157	10	2.713 sh	8		
4.033	**49**	2.644 b	5		
3.940	12	2.611 b	7		

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

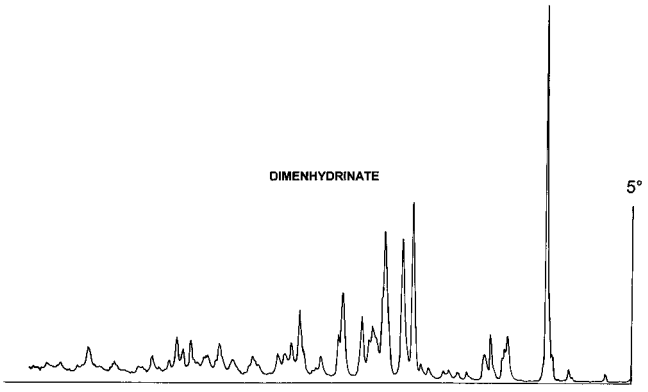

Figure 5. X-ray powder diffraction pattern of dimenhydrinate.

Results and Discussion

Tables 1−6 and Figures 1−12 show the data and the X-ray patterns obtained for the 12 drugs in current use in terms of the lattice spacings and the relative intensities of the lines. These, which characterize the 12 drugs, 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 of 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.

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

d/Å	I/I_0	*d*/Å	I/I_0
Oxprenolol Hydrochloride			
10.178	**100**	3.502	4
7.468	7	3.378	4
6.411	1	3.259	2
5.942	6	3.213	2
5.489	6	3.088	5
5.096	4	2.995	3
4.962	**18**	2.852	4
4.776	2	2.685	3
4.622	8	2.592	7
4.368	8	2.530	7
4.248	1	2.304	5
4.033	6	2.089	5
3.732	10	2.027	4
3.700	**13**		
3.663 sh	5		
3.606 sh	6		
3.556	3		
Oxybuprocaine (Benoxinate) Hydrochloride			
11.363	**100**	3.484	6
10.648	5	**3.388**	**29**
7.107	6	3.196	8
6.009	4	3.125	9
5.397	9	3.089	6
4.859	9	2.741	5
4.739	8	2.463	7
4.621	15		
4.462	10		
4.300 sh	8		
4.240	**32**		
4.201 sh	10		
3.771	25		
3.720	8		
3.637 sh	10		
3.614	22		
3.553	7		

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

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
Primidone					
10.872	3	3.332	7		
7.337	**100**	3.200	8		
6.579	19	3.158 b	5 b		
6.249	2	3.124 b	5		
5.975	12	3.001 sh	7sh		
5.692	5	2.977	10		
5.438	13	2.837 sh	9		
4.963 dbt	7	2.817	10		
4.829 dbt	20	2.723 b	4		
4.643	2	2.647	4		
4.444	15	2.551	5		
4.072	4	2.441	4		
3.874	**59**	2.331	5		
3.727 dbt	15	2.198	6		
3.666 dbt	**26**	2.028	8		
3.560	5				
3.391	5				
Thiomersal Na					
14.402	64	5.270	11	3.394	20
12.595	**90**	5.102	19	3.336	39
10.339 b	4	4.836 sh	43	3.283	27
9.623	79	**4.788** dbt	**100**	3.252	28
9.041	14	4.663 dbt	42	3.198	41
7.900	16	4.585 sh	12	3.168	29
7.714 sh	5	4.511 b	11	3.132	59
7.385 sh	18	4.398 b	16	3.067	39
7.189 dbt	**95**	4.298	63	3.001	27
6.925 dbt	40	4.117	29	2.943	29
6.755 sh	5	3.997 sh	19	2.803	45
6.525 b	6	3.947	53	2.770 sh	19
6.335 b	8	3.864 sh	17	2.723	41
6.099 b	7	3.687	19	2.678	20
6.032 b	7	3.553	36	2.550	24
5.688 b	8	3.500	24	2.460	23
5.520	28	3.453	19	2.438	25

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

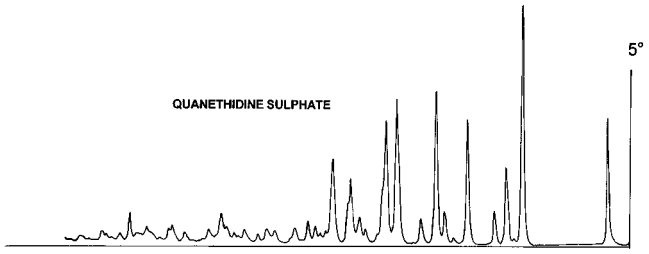

Figure 6. X-ray powder diffraction pattern of quanethidine sulphate.

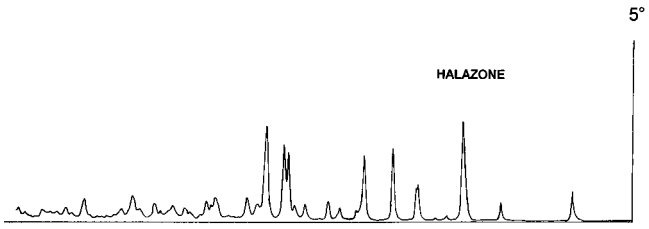

Figure 7. X-ray powder diffraction pattern of halazone.

In atenolol the three most intense lines are observed at 13.795 Å (100), 4.312 Å,[34] and 9.191 Å[31] corresponding to 2θ values of 6.407°, 20.596°, and 9.623°, respectively. In the back-loading method, the lines at 4.999 Å and 4.851 Å are of equal heights (doublet) whereas, in the side drift technique, the first line at 4.982 Å appears as a prominent shoulder attached to the stonger in intensity line at 4.845 Å. Similarly, the lines at 3.727 Å (3.713 Å) and 3.647 Å

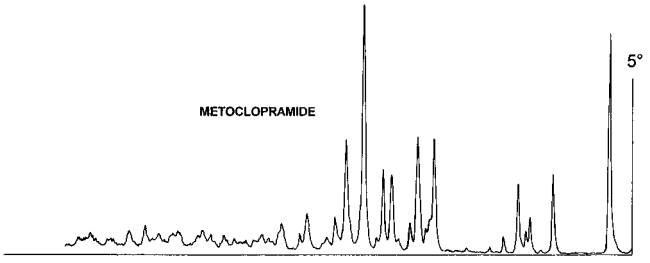

Figure 8. X-ray powder diffraction pattern of metoclopramide.

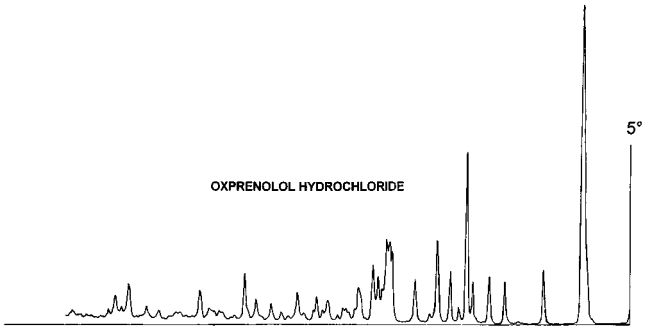

Figure 9. X-ray powder diffraction pattern of oxprenolol hydrochloride.

(3.628 Å) vary in intensity between the two methods of loading the samples (Figure 1), showing the discrepancies which are observed between the two methods of loading the sample.

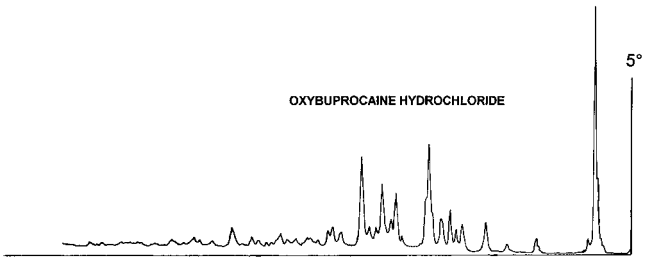

Figure 10. X-ray powder diffraction pattern of oxybuprocaine hydrochloride.

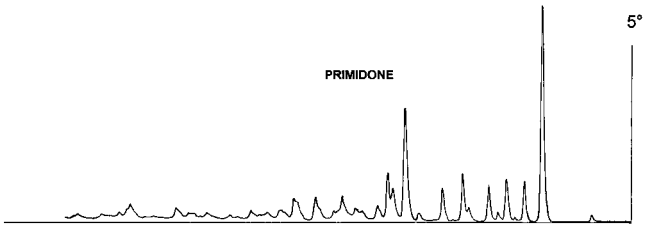

Figure 11. X-ray powder diffraction pattern of primidone.

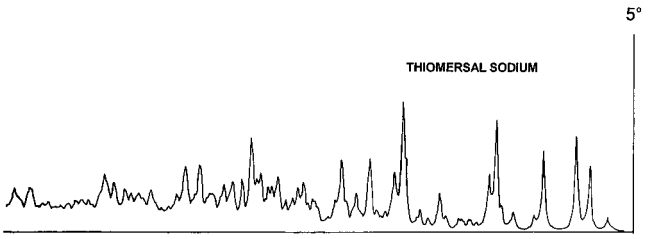

Figure 12. X-ray powder diffraction pattern of thiomersal.

In benactyzine HCl the most prominent lines occur in the angular areas 15−17° and 22°−25° 2θ, corresponding to the *d* spacing ranges 5.788−4.866 Å and 3.965−3.439 Å, respectively. Parts a and b of Figure 2 show the patterns derived from the two methods of loading the samples. The McCreery method gives more consistent and reproducible results, whereas the most intense peak with *d* spacing in the Byström−Asklund method occurs in the *d* spacing 5.267 Å (16.8322θ). Other lines can also vary in shape and intensity.

Dicyclomine HCl (dicycloverine HCl) is characterized by eigth intense lines at 15.800 (15.852), 5.298 (5.309), 5.089 (5.090), 3.972 (3.985) [with a shoulder at 3.927 (3.939) Å], 3.745 (3.752), 3.182 (3.190), 2.681 (2.683), and 2.653 (2.657), which include the three most intense lines. Some of them are very reproducible, whereas others vary with the method of loading the sample. The values in parentheses show the data derived from the side-loaded method.

The pattern of dyclonine HCl reveals three very characteristic doublets at 4.887−4.761, 4.044−3.980, and 2.378−2.346 Å which are little affected with the method of loading the sample. Other intense lines appear at 14.288, 6.391 and 3.586, and 3.323 and 2.856 Å.

For dimenhydrinate a cluster of characteristic peaks occurs in the angular region 19−27° 2θ (4.553−3.188 Å). Also the intense peak at 8.320 Å is very characteristic of the compound.

Guanethidine sulfate yields very reproducible patterns. It was observed that the patterns derived from the side-loaded method were characterized by sharp and prominent lines. Some of the lines appear at 13.042, 6.516, 4.944, 4.497, 4.341, 3.772, 3.646, 3.372, 2.279, and 3.121 Å *d* spacings.

Halazone exhibits a doublet at 3.274−3.240 Å which is included among the strongest peaks in the pattern. Other lines at 5.542, 4.332, 3.975, and 3.111 Å can be affected by the method of preparing the sample.

In metoclopramide the line 13.038 Å, at very low angle (6.78°), can vary considerably in intensity among different methods of loading the sample, and this is an indication that the crystalline material suffers from preferred orientation. Other intense peaks appear at 4.279, 4.033, 3.388, and 3.220 Å and can vary in intensity according to the sample preparation.

The features of oxprenolol HCl are a very strong line at 10.178 Å and a complex of unresolved lines in the angular range 22−26° 2θ (4.033−3.378 Å range of *d* spacings) which are little affected by the method of packing the sample. Other characteristic strong lines occur at 7.468, 5.942, 5.489, 4.962, and 4.368 Å.

Oxybuprocaine HCl yields two clusters of peaks in the angular ranges 18−21 and 23−27° 2θ. Also, the strongest line at 11.363 Å *d* spacing is very characteristic of the compound. Other characteristic peaks occur at 3.771, 4.240, 3.388, and 3.614 Å *d* spacings.

Primidone shows two doublets at 4.963−4.829 and 3.727−3.666 Å *d* spacing. The intensity of the first line at 4.963 Å can vary with the method of packing the sample and sometimes appears as a shoulder attached to the line at 4.829 Å. Also, the lines at 7.337, 6.579, 5.975, 5.438, 4.444, and 3.874 Å can vary in intensity with the method of packing the samples.

The thiomersal (thimerosal) pattern contains numerous compact but characteristic peaks in the angular range 24−34° 2θ which are very reproducible using different methods of loading the samples. Also two doublets at 7.189−6.925 and 4.788−4.663 Å *d* spacing are very prominent and reproducible in the pattern.

In conclusion, the data presented show no fundamental discrepancies in the *d* spacings. Differences in the intensies of the most characteristic and important peaks in the diffraction patterns have been described and pointed out. Different runs of several sample loadings have proved that the results are reproducible and therefore acceptable.

Registry Numbers of the Drug Substances (CAS Numbers) (Supplied by the Authors). Atenolol, 29122-68-7, 60 966-51-0; benactyzine hydrochloride, 57-37-4; dicylomine hydrochloride, 67-92-5; dyclonine hydrochloride, 536-43-6; dimenhydrinate, 523-87-5; guanethidine sulfate, 645-43-2; halazone, 80-13-7; metoclopramide, 364-62-5; oxprenolol hydrochloride, 6453-73-9; oxybuprocaine hydrochloride, 5987-82-6; primidone, 125-33-7; thiomersal sodium, 54-648.

Literature Cited

(1) Hanawalt, J. D.; Rinn, H. W. Identification of Crystalline Materials—Classification and Use of X-ray Diffraction Patterns. *Powder Diffr.* **1986**, *1*, 2−6.

(2) Koundourellis, J. E.; Malliou, E. T.; Sullivan, R. A. L.; Chapman, B. X-ray Characterization of 12 Vasodilators in Current Use. *J. Chem. Eng. Data* **1999**, *44* (4), 656−660.

(3) United States Pharmacopeia XXII and National Formulary XVII, 1990, pp 1621−1623.

(4) Phadnis, N. V.; Caratur, R. K.; Suryanarayanan, R. Identification of drugs in pharmaceutical dosage forms by X-ray powder defraction. *J. Pharm. Biomed. Anal.* **1997**, *15*, 929−943.

(5) Doff, D. H.; Brownen, F. L.; Corrigan, O. I. Determination of α-Impurities in the β-Polymorph of Inosine Using Infrared Spectroscopy and X-ray Powder Diffraction. *Analyst* **1986**, *111*, 179−182.

(6) Bartolomei, M.; Ramusino, C. M.; Ghett, P. Solid-state investigation of fluocinolone acetonide. *J. Pharm. Biomed. Anal.* **1997**, *15*, 1813−1820.

(7) Matsunage, H.; Eguchi, T.; Nishijima, K.; Enomoto, T.; Sasaoki, K.; Nakamura, N. Solid-state characterization of candesartan cilexetil (TCV-116): Crystal structure and molecular mobility. *Chem. Pharm. Bull.* **1999**, *47* (2), 182−186.

(8) Hassan, M. A.; Sheikh-Salem, M.; Sallam, E.; Al-Hindawi, M. K. Preparation and characterization of a new polymorphic form and a solvate of glibenclamide. *Acta Pharm. Hung.* **1007**, *67*, 81−88.
(9) Nichols, G.; Frampton, C. S. Physicochemical Characterization of the orthorhombic polymorph of paracetamol crystallized from solution. *J. Pharm. Sci.* **1998**, *87*, 684−693.
(10) DiMartino, P.; Conflant, P.; Drache, M.; Huvenne, J. P.; Guyot-Hermann, A. M. Preparation and physical characterization of forms II and III of paracetamol. *J. Therm. Anal.* **1997**, *48*, 447−458.
(11) Liebenberg, W.; de Villiers, M. M.; Wurster, D. E.; Swanepoel, E.; Dekker, T. G.; Lotter, A. P. The effect of polymorphism comparison and dissolution properties of chemically equivalent oxytetracycline hydrochloride powders. *Drug Dev. Ind. Pharm.* **1999**, *25* (9), 1027−1033.
(12) Elks, J.; Ganellin, G. R. *Dictionary of Drugs, Chemicals Data, Structures and Bibliographies;* Chapman and Hall Ltd.: London, 1990.
(13) Moffat, A. C., Ed. *Clarke's Isolation and Identification of Drugs;* The Pharmaceutical Press: London, 1986.
(14) *British Pharmacopoeia*; London, 1993.
(15) Klug and Alexander. *X-ray diffraction procedures*, 2nd ed.; Wiley & Son: New York, 1974; p 372.

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