$CH_2N<$, 2H, triplet, $J=6$ Hz), 3.45 ($CH_2CH_2N<$, 2H, triplet, $J=6$ Hz), 6.70—7.20 (Ar-H, 4H, multiplet). Mass Spectrum *m/e*: 290 (M^+).

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Quantitative Analysis of Pharmaceutical Preparations by X-Ray Diffractometry. X.[1] Direct Quantitative X-Ray Diffraction Analysis of Ethionamide in Rectal Suppositories

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In the preceding paper,[1] the direct X-ray diffraction analysis was reported which seems to be useful for the assay of salicylic acid in plasters. The use of this assay method was successful in the determination of ethionamide (2-ethyl-thioisonicotinamide) in a rectal suppository, and it was found that this procedure is rapid and reliable.

Experimental

X-Ray Equipment——For the experimental work, a Rigakudenki Geigerflex diffractometer was used. X-Ray source was a copper-target X-ray tube with a Ni-foil filter. The slit system used in this work was a divergence slit 1°, scatter slit 1°, and recieving slit 0.3 mm. The time constant of rate-meter was 2 sec. A Geiger Müller tube was used as a detection device. The scanning speed of goniometer was 1/4° (2θ) per minute, and the chart speed was adjusted to be 2 cm/min throughout this work.

Preparation of Standard Rectal Suppositories——Known amounts of ethionamide and suppository bases were weighed accurately. For the suppository bases, 8 parts of polyethylene glycol 4000 and 2 parts of polyethylene glycol 400 were used. The mixture was melted on a water bath and poured into the hinged suppository molds cooled in blocks of ice.

Quantitative Analysis of Ethionamide in Suppositories——The rectal suppository was placed on the center of a cardboard (a backing) and covered with a sheet of cellophane paper (a facing), and pressed with a hydraulic press under various molding pressure at 40° for 5 min. The cellophane paper was stripped off and the cardboard was cut to size of about 3.5×6.0 cm and placed in the sepcially designed sample holder made of Bakelite, which was reported in the preceding paper.[1] The holder was set on the diffractometer and scanned.

The diffraction patterns of powdered ethionamide, placebo rectal suppository, and ethion-

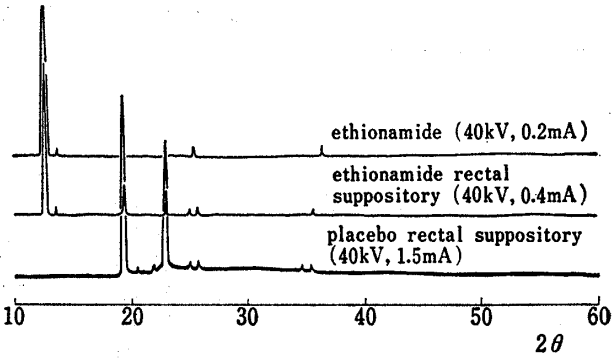

Fig. 1. X-Ray Diffraction Patterns of Ethionamide, Ethionamide Rectal Suppository, and Placebo Rectal Suppository

1) Part IX: K. Kuroda, G. Hashizume, and F. Kume, *Chem. Pharm. Bull.* (Tokyo), 17, 818 (1969).
2) Location: *a) Kusunoki-cho, Ikuta-ku, Kobe, 650, Japan; b) Yukihira-cho, Suma-ku, Kobe, 654, Japan.*

amide rectal suppository on market are shwon in Fig. 1, which show that the diffraction peak at 11.8° (2θ) is due to crystalline ethionamide and the peak intensity is not influenced by other peaks. The peak at 11.8° (2θ), therefore, was chosen as a basis for the determination.

For each synthetic standard suppository, the diffraction peak height and/or the peak area intensity was measured. The standard curves were prepared by plotting the compositions against the relative diffraction peak intensities, and are shown in Fig. 2.

The relationship between diffraction peak intensities and molding pressures is shown in Fig. 3, and Table I shows the linearity of the intensities for the samples prepared under various molding pressures.

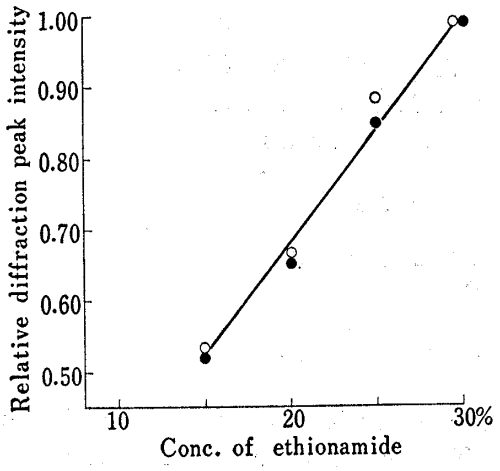

Fig. 2. Calibration Curves for Ethionamide in Rectal Suppository

—○—: by peak height
—●—: by peak area[a)]
a) peak height (cm) × scanning time (sec)/2

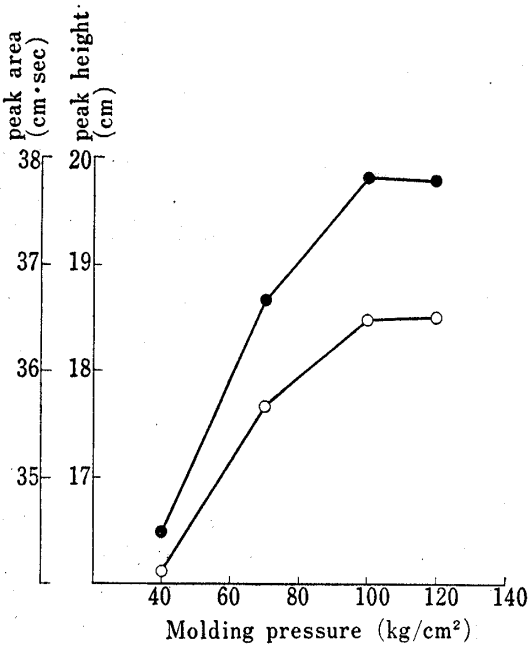

Fig. 3. Relationship between Diffraction Peak Intensity and Molding Pressure

—○—: by peak height
—●—: by peak area

The reproducibility of the measurements made for a suppository placed at various sites in the holder s shown in Table II. The reproducibility of observed values in repeated observations of four suppositories

Table I. Lineality of the Intensities Measured on the Suppositories Prepared under Various Molding Pressures

	Peak intensity measured by					
	Height			Area		
Molding pressure (kg/cm²)	40	70	120	40	70	120
	14.30	16.68	17.57	33.03	37.03	37.68
	17.68	19.70	18.44	37.66	37.23	40.09
	15.52	17.70	17.58	34.92	35.92	37.62
	13.79	18.38	16.64	33.79	37.50	35.95
	18.02	16.87	17.50	37.84	36.78	38.33
	15.99	17.83	18.90	31.66	35.84	27.99
	17.87	16.77	18.88	37.17	38.74	36.75
	18.36	16.87	18.82	34.88	36.27	36.77
	14.63	18.22	21.21	30.87	34.62	40.08
	15.14	18.20	19.83	32.70	36.76	36.55
Av.	16.13	17.72	18.54	34.52	36.67	37.78
S.D. (%)	10.62	5.34	7.12	7.21	3.02	3.74

is summarized in Table III. Table IV is a comparison of diffraction and chemical analysis[3] of six standard ethionamide rectal suppositories.

Table II. Reproducibility of the Measurements for a Suppository Placed in the Holder

Peak intensities measured by		Peak intensities measured by	
Ht., cm	Area, cm·sec	Ht., cm	Area, cm·sec
15.70	40.19	18.74	38.99
16.16	35.71	17.66	37.62
16.16	35.23	18.98	39.12
16.93	35.38	18.72	39.13
16.53	37.36	Av. 17.31	37.51
17.58	36.39	S.D. (%) 6.94	4.77

Table III. Reproducibility of the Observed Intensities in Repeated Observations of Four Ethionamide Rectal Suppositories

Supp. No.	1		2		3		4	
	Peak Ht.	Peak Area	Peak Ht.	Peak Area	Peak Ht.	Peak Area	Peak Ht.	Peak Area
	18.33	40.69	18.27	40.46	18.13	40.28	17.80	39.85
	20.56	41.94	19.09	41.06	18.76	40.22	18.70	40.06
	19.58	37.59	18.26	37.51	18.70	37.89	18.55	38.33
	16.07	37.60	17.79	37.04	18.16	37.54	18.45	38.60
	19.26	37.75	18.53	39.08	18.91	39.29	18.98	39.63
	17.10	37.96	17.49	39.00	17.25	37.76	17.37	38.20
	18.17	38.52	18.88	39.04	18.94	40.45	18.78	39.99
	18.00	39.06	17.35	38.49	18.02	38.63	17.87	39.02
	19.56	35.40	19.11	37.30	18.84	38.22	18.56	38.40
	16.77	37.73	17.34	38.11	17.89	40.49	17.58	39.98
Av.	18.34	37.72	18.21	38.71	18.36	39.08	18.26	39.21
S.D. (%)	7.73	6.41	3.81	3.39	3.04	3.09	3.06	1.97

Table IV. Comparison of Diffraction and Chemical Analyses of Individual Standard Ethionamide Rectal Suppositories

Suppositories number	Diffraction analysis[a] (%)	Diviation from the mean (%)	Chemical analysis[b] (%)	Diviation from the mean (%)
1	96.6	0.5	97.2	0.5
2	97.7	0.6	97.6	0.1
3	97.6	0.5	97.3	0.4
4	99.0	1.9	99.2	1.5
5	96.6	0.5	98.1	0.5
6	95.6	1.5	96.9	0.8
Mean	97.1	0.9	97.7	0.6

a) measured by peak area intensity *b*) measured by Codex Medicamentarius Gallicus

Result and Discussion

It was at first found that a marked error is introduced by the setting of the sample in a holder. This error was found to be due to a small bending of the sample plate surface, since the back was too thin. A card-board of about 0.5 mm thickness was, therefore, used as the backing throughout this work.

3) "Codex Medicamentarius Gallicus (Codex Français)," 1965 p. 439.

It was also found, as shown in Fig. 3, that the diffraction intensity increased with increase in the molding pressure and that the diffraction intensity became almost constant when the molding pressure was increased more than 100 kg/cm^2. Since the sample plate is fairly thick, the pressure effect of the dispersion of crystallites, crystal size distribution, and the thickness of matrix might be neglected. This pressure effect, therefore, might be due to the preferred orientation of the crystallites. In the present work, the molding pressure of 120 kg/cm^2 was chosen. The linearity of the measurements for the samples prepared under this pressure was better than that at 70 kg/cm^2 pressure, as shown in Table I.

It will be seen from the results shown in Table II and III that a better reproducibility is obtained by the use of the peak area intensity than by the use of the peak height intensity.

From the results of Table IV, it can be concluded that this method is as sensitive as the conventional chemical method. Furthermore, only 3 hr are needed to assay 6 ethionamide rectal suppositories, while the chemical method takes about 1 day.

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