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STUDIES ON SPIRONOLACTONE POLYMORPHIC FORMS

by

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ABSTRACT

The phenomenon of polymorphism of spironolactone was studied using melting point and aqueous solubility determinations, infrared spectroscopy, differential thermal analysis, X-ray powder diffraction and powder dissolution. The results showed that spironolactone crystals obtained from ethyl acetate had the lowest melting range, while those obtained from acetonitrile had the highest range. The aqueous solubility data indicated the presence of different forms of spironolactone, each with a specific solubility, although practically all of these forms could be considered to be water-insoluble. The infrared spectra were not useful in clearly distinguishing between

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the different forms. Differential thermal analysis curves indicated that some of the forms obtained by treating spironolactone with different solvents were somewhat similar, others were variable, but all of them were different from the original form of the drug. Moreover, the thermal study proved the absence of any solvates. X-ray patterns were different in spacing (d) values and intensities of radiation absorption, confirming the presence of four different forms of spironolactone. The form obtained from ethyl acetate had the highest dissolution rate, while that obtained from acetonitrile had the lowest rate.

Spironolactone is known to crystallize out from different solvents in different polymorphic forms and to undergo structural rearrangements on heating.[1,2] The study was mainly concerned with the infrared identification of steroids, and the results showed that sample preparation techniques have a profound effect on the spectra of these steroids.

Florence and Salole[3] undertook a brief investigation into the effects of grinding on the crystalline properties of spironolactone. The results showed no major changes in infrared spectrum after grinding, apart from a decrease in resolution of the absorption peaks. The premelting behavior of the drug was altered, which would indicate that grinding significantly affected the spironolactone crystallinity.

El-dalsh *et al.*[4] showed that spironolactone co-precipitate with povidone using different solvents such as

absolute ethyl alcohol, acetonitrile and chloroform had a different X-ray diffraction pattern which may be explained on the basis of various polymorphic forms.

The purpose of the present work is to carry out studies to specify the number of polymorphs of spironolactone under the crystallization conditions.

EXPERIMENTAL

Preparation of Spironolactone Polymorphs: This was carried out by dissolving spironolactone† in either absolute ethyl alcohol, acetonitrile, chloroform or ethyl acetate in sufficient amounts to produce supersaturated solutions on heating. The hot solutions were filtered, and cooled to room temperature. The crystals separated were filtered and were dried in a desiccator over calcium chloride for one week before use.

Melting Point Determination: The melting points of the separated crystals were determined using a Kofler microscope. The temperature at which the crystals began to melt and that of completed melting were recorded.

Equilibrium Solubility Determination: The determination of solubility was carried out by placing an excess amount of each of the tested samples with 15 ml of distilled water in 25 ml capacity sealed glass ampoules. The mixtures were rotated for 48 hours in a constant temperature water bath at 29 ± 1° C, and then filtered through a 0.45 mμ Millipore filter. One ml of the filtrate was

†G. D. Searle Co., Ltd., Morpeth, England.

diluted to 10 ml with a water/methanol mixture (such that the water/methanol concentration was 20% v/v) and spironolactone was spectrophotometrically determined at 242 nm. The equilibrium solubility was calculated from a standard calibration curve.

Infrared (IR) Spectral Study: The IR spectrum for each sample was determined using a potassium bromide pellet technique and a Beckman IR spectrophotometer.†

Differential Thermal Analysis (DTA) Study: The DTA curves were measured for each of the prepared samples. An accurately weighed sample (0.1 g) was thermally treated using aluminum oxide as a reference material in the derivatograph.†† The conditions of analysis were: the sensitivity of the galvanometer was 1/10, the heating rate was 20° C per minute, and the time was 25 min. The temperature of the sample to be examined was raised starting from room temperature.

X-ray Powder Diffraction Study: The X-ray diffraction patterns of the different samples were measured utilizing a diffractometer.† The diffracted copper radiation of wave length 1.54 Å, filtered by nickel, was detected by a scintillation counter and was automatically recorded.

Powder Dissolution Study: The dissolution was performed by the addition of 100 mg of each sample to 100 ml dis-

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†Acculab-6, Beckman, Fullerton, California, U.S.A.

††MOM #085838, Hungary.

†D500, Siemens, West Germany.

tilled water in a 250 ml beaker immersed in a thermostatically controlled water bath at 37 ± 0.5° C. The mixture was stirred at 100 rpm with a propellor stirrer. At predetermined time intervals, a sample of 1 ml was withdrawn through a sintered glass filter assembly. The volume taken was immediately replaced by an equal amount of distilled water heated to the same temperature. The sample taken was diluted to 10 ml with aqueous methanol solution (such that water/methanol concentration was 20% v/v) and the drug was spectrophotometrically determined at 242 nm.

RESULTS AND DISCUSSION

Table 1 showed that each residue has a different melting range, some of which are more variable from that of the untreated drug. Moreover, the determination of aqueous solutility of each of these residues indicated

TABLE 1

MELTING RANGES AND AQUEOUS SOLUBILITY OF SPIRONOLACTONE TREATED WITH DIFFERENT SOLVENTS

Solvent	Melting Range (°C)	Aqueous Solubility (lit/gm)
---	205-207	37.0
Absolute Ethyl alcohol	208-210	23.2
Acetonitrile	210-212	34.5
Chloroform	205-207	22.2
Ethyl acetate	200-202	18.2

the presence of different forms of spironolactone, each with a specific melting range and aqueous solubility. All these forms can be considered to be equally hydrophobic. However, the polymorphs obtained can be arranged according to their melting point into the following descending order: that obtained from acetonitrile, absolute ethyl alcohol, chloroform and that obtained from ethyl acetate.

The infrared data were unsuccessful in clearly distinguishing between the different forms. No marked change was noticed in the spectra of the drug treated with either absolute ethyl alcohol, acetonitrile or chloroform (Fig. 2-3). In the case of spironolactone treated with ethyl acetate, the spectrum (Figure 5) was identical to that of the untreated drug (Figure 1) with the exception of the appearance of a new peak in the region between 3400 to 3500 cm^{-1}, which is usually due to O-H stretching vibrations. The development or disappearance of these new frequencies can also be explained on the basis that the grinding process carried out for preparing the infrared scanning samples may destroy the crystallinity, especially if it is of a temporary type. The same explanation was given by Florence and Salole.[3]

The differential thermal analysis data (Figure 6) showed some similarity between the thermograms given by the drug crystallized from absolute ethyl alcohol and acetonitrile. The endothermic peak in the first case was at 129° C, while there were two peaks at 120° and

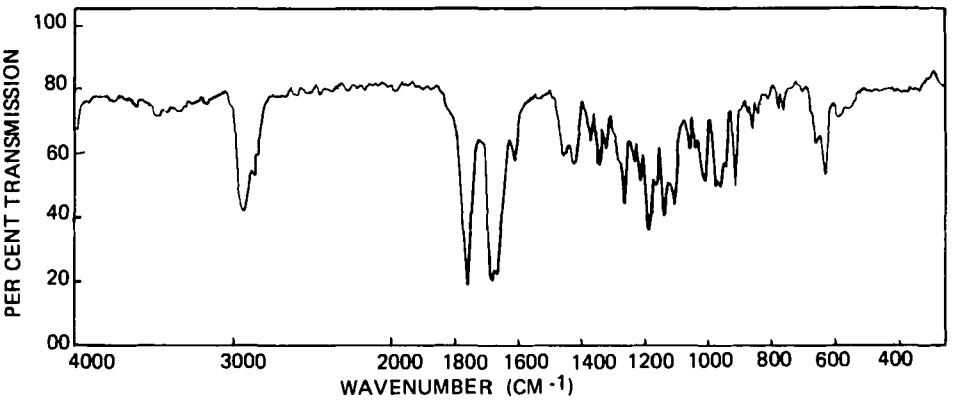

__FIGURE I__

INFRARED SPECTRUM OF SPIRONOLACTONE.

148° C in the other case. Thermograms of spironolactone recrystallized from chloroform and ethyl acetate were somewhat similar and differed from those of untreated drug or drug crystallized from absolute ethyl alcohol or acetonitrile. These results indicate the presence of four different forms of the drug. Moreover, the thermal behavior showed the absence of any solvate form of the drug.

The results in Table 2 and Figures 7-10 showed that the X-ray pattern of the drug depends on the solvent from which it is crystallized. Spacing values (d) and intensities of radiation absorption were different for peaks from each residue, indicating a different crystal lattice.

The dissolution data (Figure 11) showed that the residue obtained after treatment of spironolactone with ethyl acetate had the highest dissolution rate, while

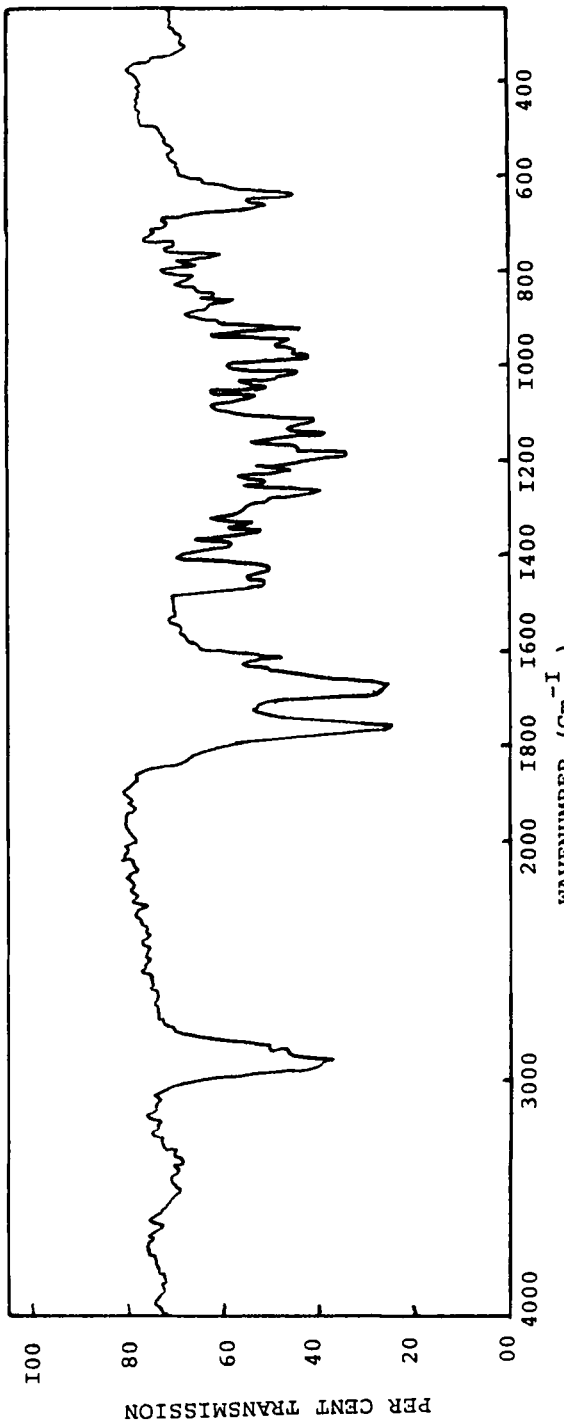

FIGURE 2

INFRARED SPECTRUM OF SPIRONOLACTONE CRYSTALLIZED FROM ABSOLUTE ETHYL ALCOHOL

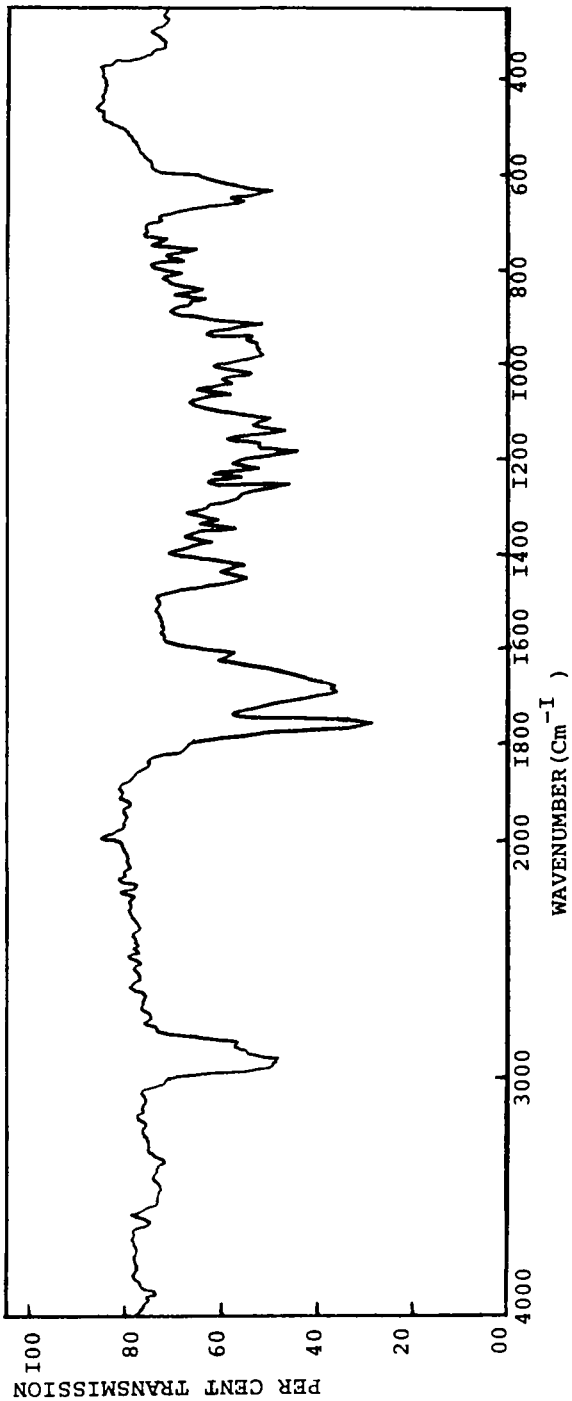

FIGURE 3

INFRARED SPECTRUM OF SPIRONOLACTONE CRYSTALLIZED FROM ACETONITRILE.

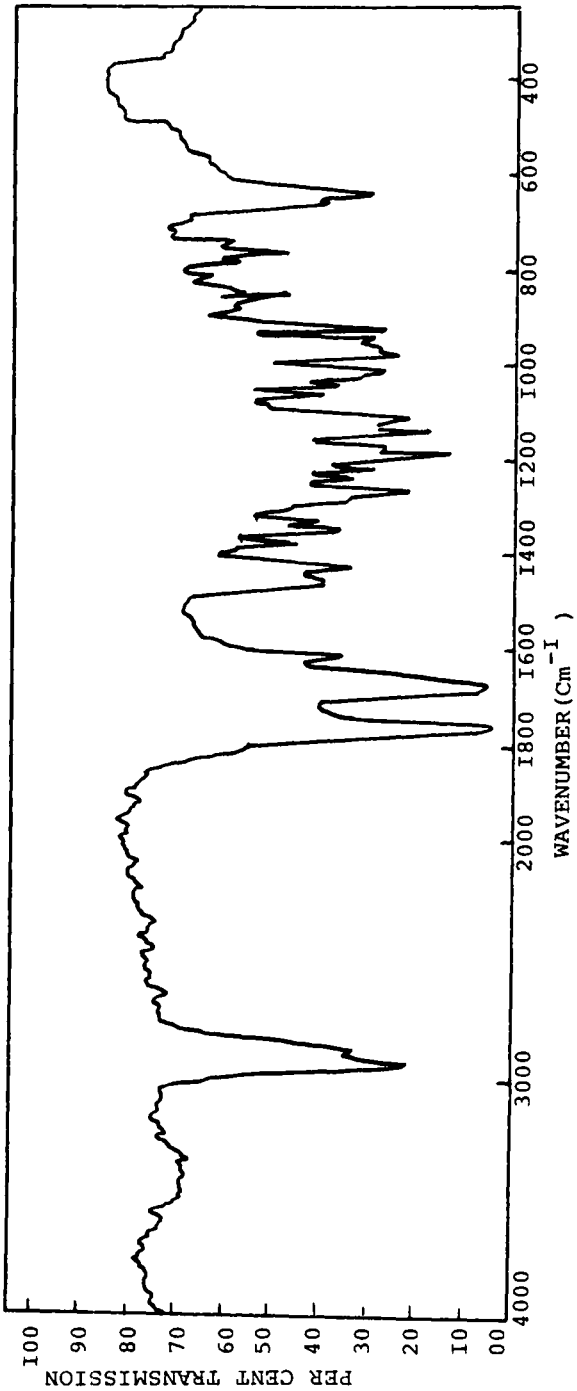

FIGURE 4

INFRARED SPECTRUM OF SPIRONOLACTONE CRYSTALLIZED FROM CHLOROFORM.

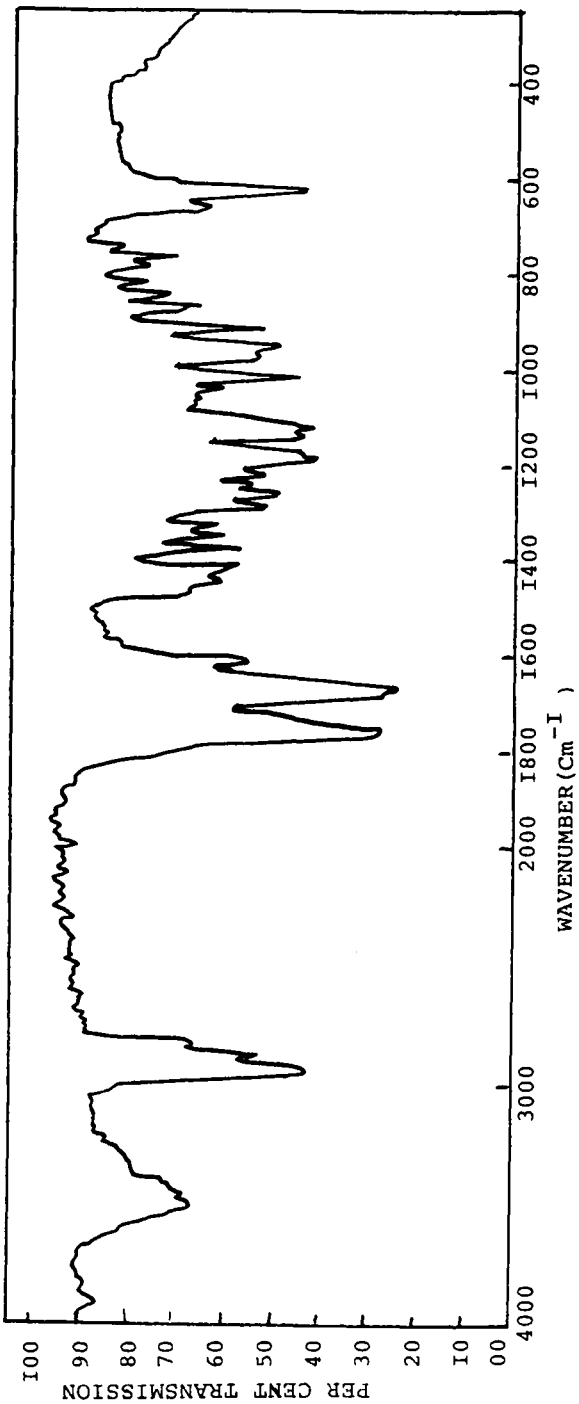

FIGURE 5

INFRARED SPECTRUM OF SPIRONOLACTONE CRYSTALLIZED FROM ETHYL ACETATE.

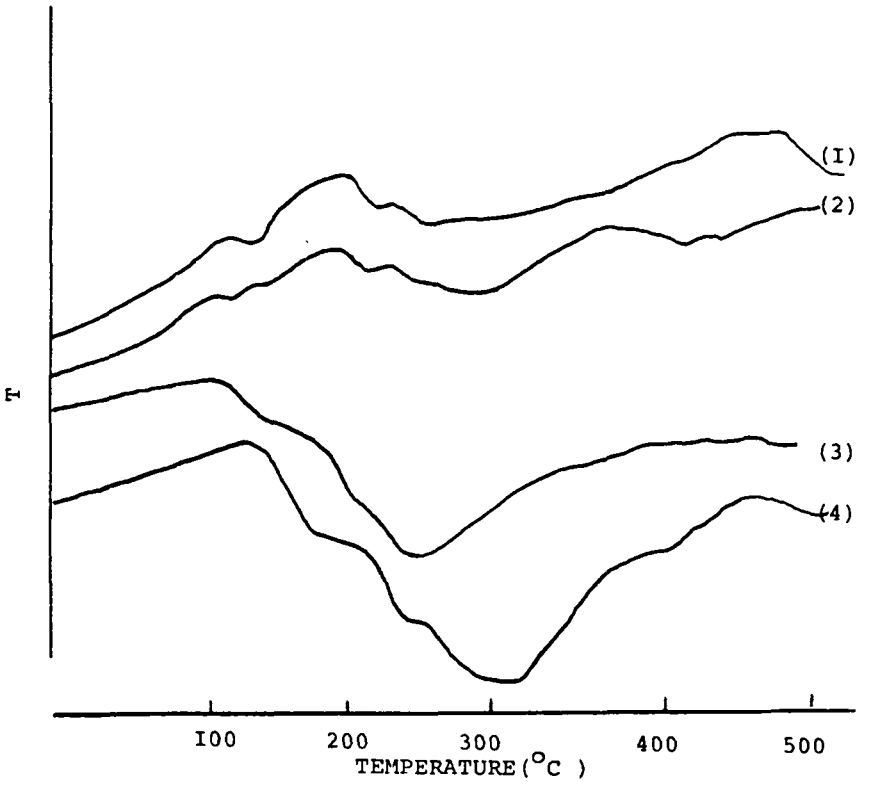

FIGURE 6

DIFFERENTIAL THERMAL ANALYSIS CURVES OF SPIRONOLACTONE CRYSTALLIZED FROM ABSOLUTE ETHYL ALCOHOL(I),ACETONITRILE(2),CHLOROFORM (3),AND ETHYL ACETATE(4)

that obtained after treatment with acetonitrile had the lowest rate. Those residues obtained after treatment of the drug with chloroform and ethyl alcohol had comparable dissolution rate values. The order in which the dissolution rate changes are arranged denotes the presence of a stable form of drug structure which is characterized by a steady release profile as in the case of drug treated with acetonitrile. Other forms obtained by treatment

TABLE 2

SPACING (d) VALUES OF X-RAY DIFFRACTION OF SPIRONOLACTONE

CRYSTALS OBTAINED FROM DIFFERENT SOLVENTS

Serial No. of Peaks	Spacing (d) Values of X-ray Diffraction (Å) of Spironolactone Crystals Obtained from:			
	Ethyl alcohol	Acetonitrile	Chloroform	Ethyl acetate
1	9.6 w	--	9.2 s	10.3 w
2	7.6 m	7.6 w	8.0 w	7.8 s
3	--	7.3 s	7.3 w	--
4	--	--	6.9 m	--
5	5.2 m	5.5 m	5.4 s	--
6	--	5.2 s	5.2 s	--
7	--	--	4.9 s	--
8	--	--	4.8 w	--
9	4.6 w	--	4.7 w	--
10	4.2 m	4.1 s	4.2 s	--
11	4.0 m	3.8 m	--	4.2 m
12	--	3.5 m	--	3.8 w
13	--	3.18 m	--	3.2 m
14	--	3.12 m	--	--
15	2.8 m	--	--	2.9 m
16	2.7 s	2.6 m	--	--
17	2.36 s	2.3 m	--	2.3 w
18	2.2 m	2.2 s	--	--
19	2.1 w	--	--	--
20	2.0 s	2.0 m	--	2.0 w

According to the height of the peak, the following symbols are given: s = strong; m = medium; w = weak.

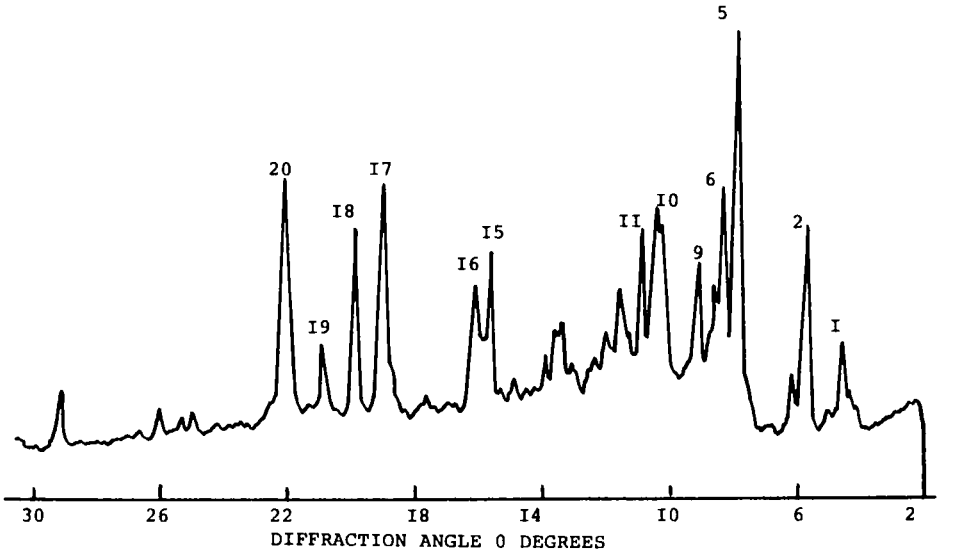

FIGURE 7

X-RAY DIFFRACTION PATTERN OF SPIRONOLACTONE CRYSTALLIZED FROM ABSOLUTE ETHYL ALCOHOL.

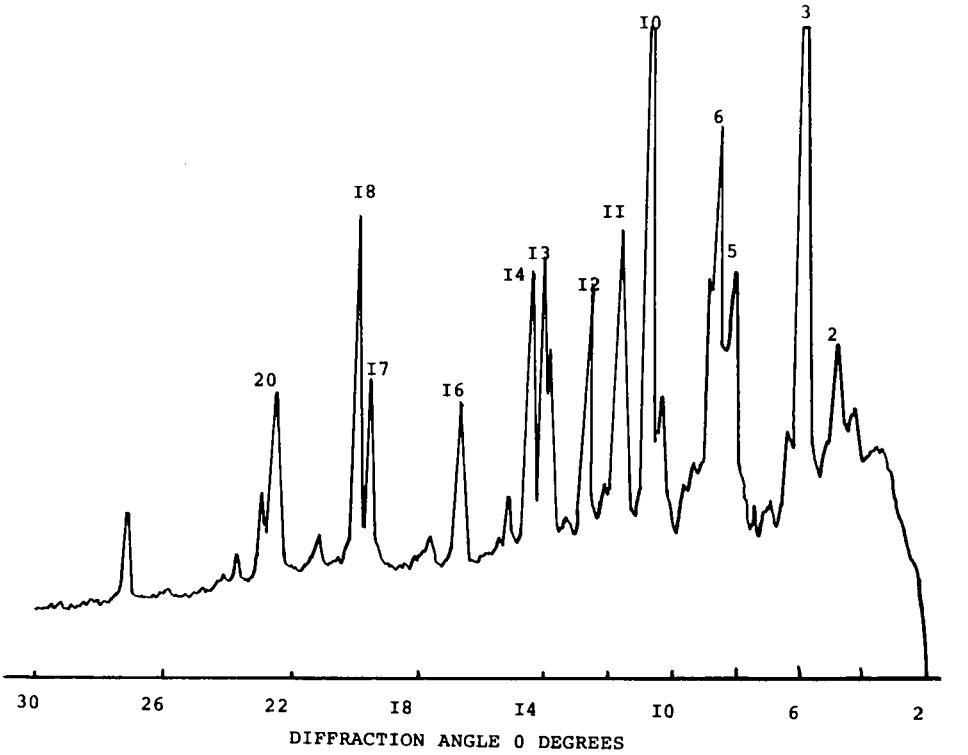

FIGURE 8

X-RAY DIFFRACTION PATTERN OF SPIRONOLACTONE CRYSTALLIZED FROM ACETONITRILE.

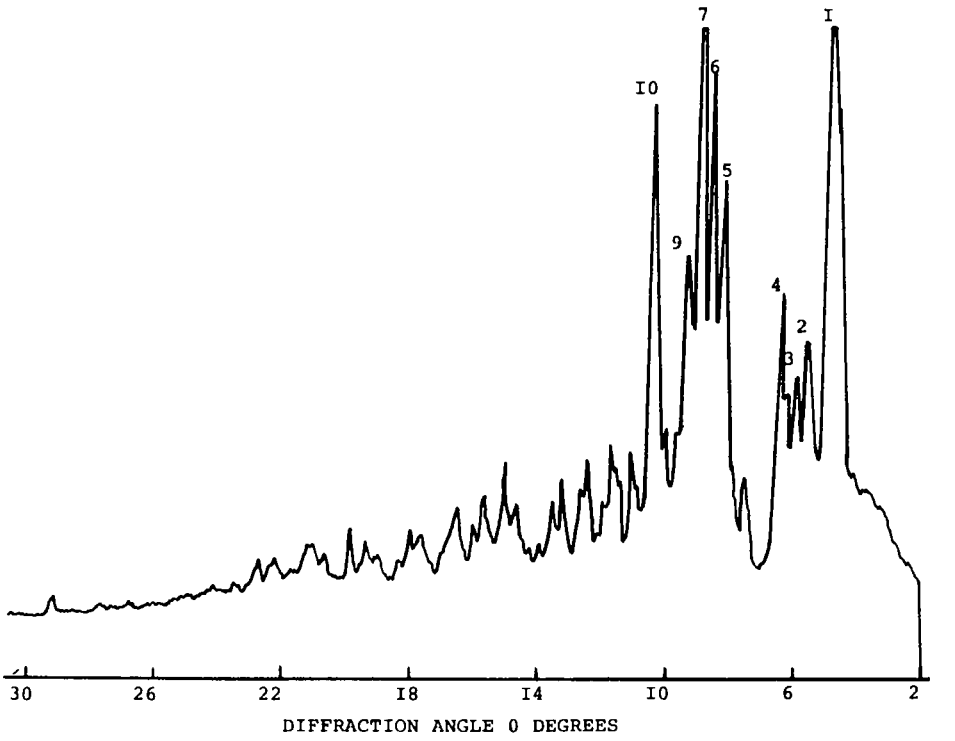

__FIGURE 9__

X-RAY DIFFRACTION PATTERN OF SPIRONOLACTONE CRYSTALLIZED FROM CHLOROFORM.

with absolute ethyl alcohol, chloroform and ethyl acetate are of metastable drug structures characterized by variable profiles of dissolution which tend to retain the original steady profile of release after a period of release time. An example of these metastable structures is the polymorph obtained from ethyl acetate. The release profile of this form dropped sharply after ninety minutes of the release time to become nearly of the same level as that profile given by the form obtained from acetonitrile. The other forms obtained from chloroform

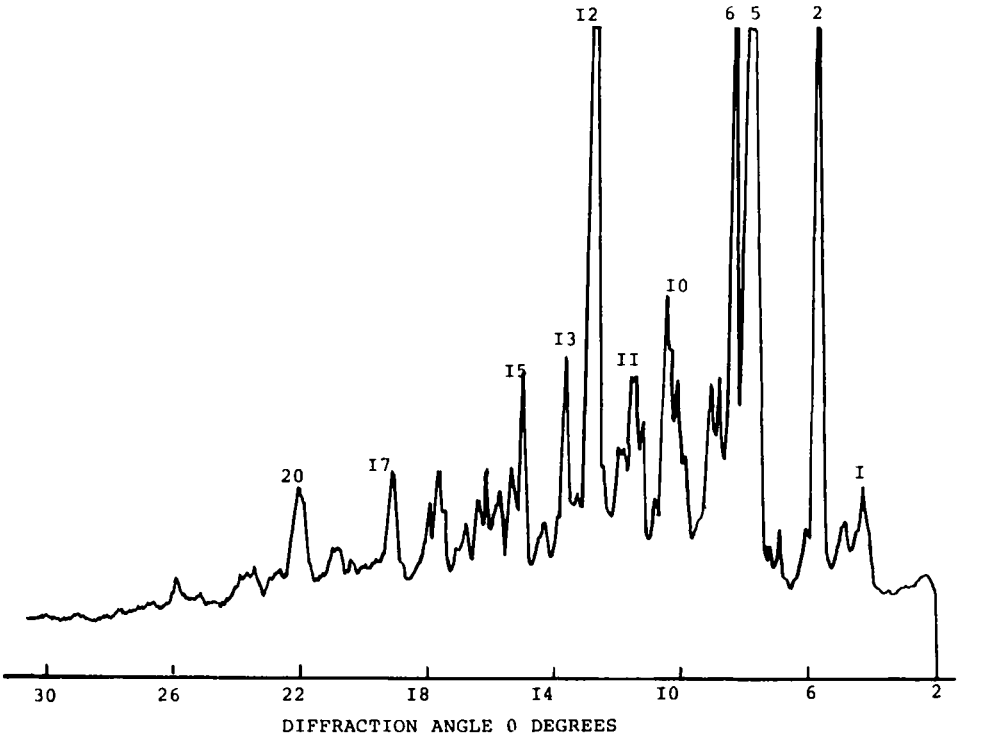

FIGURE I0

X-RAY DIFFRACTION PATTERN OF SPIRONOLACTONE CRYSTALLIZED FROM ETHYL ACETATE.

and absolute ethyl alcohol also showed the tendency of gradual change from their relatively high level of release to the original steady release profile given by the form obtained from acetonitrile. The period necessary for the completion of such a change was more than two hours in the dissolution test.

In conclusion, it can be stated that spironolactone exhibits polymorphism and can be found in four different polymorphic forms depending on the solvent of crystallization. Three of these forms, which are crystallized

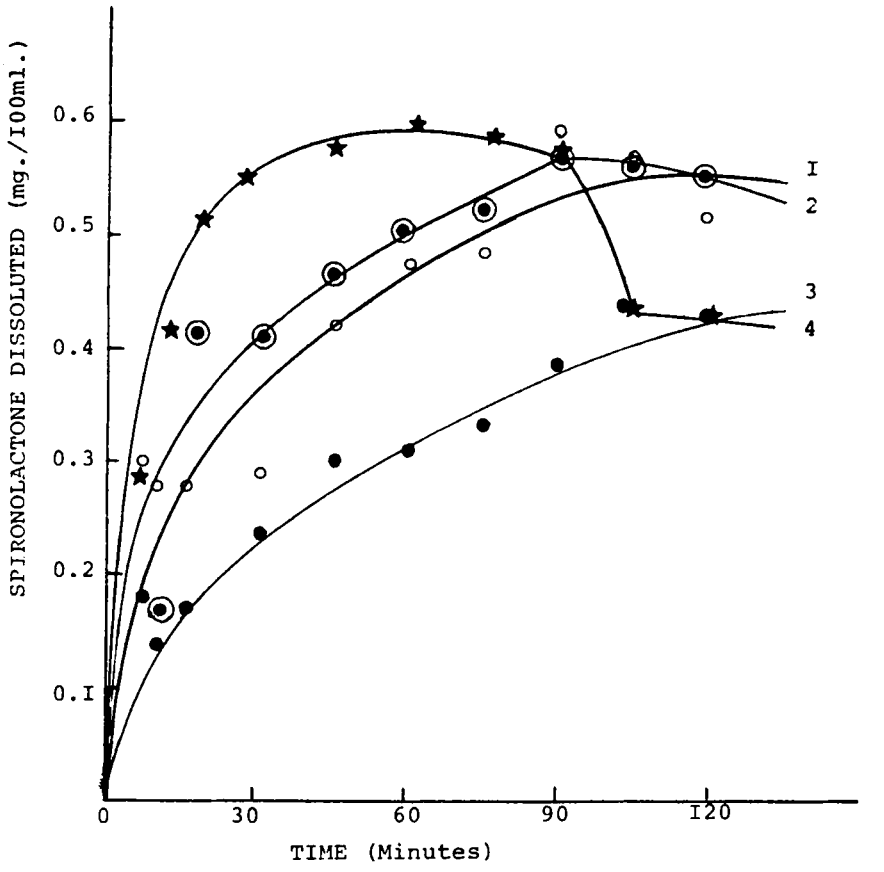

FIGURE II

DISSOLUTION PROFILES OF SPIRONOLACTONE CRYSTALLIZED FROM ABSOLUTE ETHYL ALCOHOL(I),CHLOROFORM(2), ACETONITRILE(3),AND ETHYL ACETATE(4).

from absolute ethyl alcohol, chloroform and ethyl acetate, are metastable. The stable form is that obtained by crystallization from acetonitrile.

REFERENCES

1. R. J. Mesley and C. A. Johnson, J. Pharm. Pharmacol., 17, 329 (1965).

2. J. L. Sutter and E. P. K. Lau, in "Analytical Profile of Drug Substances," Vol. 4, K. Florey, ed., Academic Press, London, 1975, pp. 431-451.

3. A. T. Florence and E. G. Salole, J. Pharm. Pharmacol., 28, 647 (1976).

4. S. S. El-dalsh, A. A. El-Sayed, A. A. Badawi, F. I. Khattab and A. Fouli, manuscript in preparation.