DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(9), 1571-1588 (1994)

PREPARATION AND CHARACTERIZATION OF RANITIDINE-HCl CRYSTALS

TARUNA MADAN & A.P. KAKKAR, COLLEGE OF PHARMACY, DELHI-17.

ABSTRACT

Four crystalline and one noncrystalline form of RANITIDINE-HCl were prepared and characterized by means of X-Ray powder diffraction, Thermal analysis (D.T.A. & T.G.A.), Polarising microscopy, Scanning electron microscopy , Infra red spectrophotometry and Ultra violet spectrophotometry. All the four crystalline forms were solvates or pseudopolymorphs. Stability determination of various forms under different conditions exhibited FORM II as most stable and all other forms convert to FORM II during storage. Humidity, Temperature and Compression force affected the polymorphic stability of various forms. Transition temperatures of different forms were determined using Equilibrium solubility method.

INTRODUCTION

Many compounds, especially complex organic molecules are capable of being manipulated to exist in more than one form as solids. Some of these forms are crystalline phases while others are metastable states where compound is in a noncrystalline form. These differnt crystalline and noncrystalline forms differ in Hygroscopicity, Physicochemical stability, Solubility and Compression behaviour.Manipulation and control of crystal form can be exploited for commercial advantage by marketing a drug in a crystal form with maximum bioavailability and longest shelflife.

EXPERIMENTAL

MATERIALS :Ranitidine HCl U.S.P. (99.5% purity) was provided by Ranbaxy Laboratories, Okhla, New Delhi. All crystallisation solvents were analytical grade.

PREPARATION OF VARIOUS FORMS : Commercial Ranitidine HCl was used in the preparation.

CRYSTALLINE FORMS [1,2] were prepared by cooling warm saturated solutions of the drug in different solvents at ($25\pm0.5^{o}C$).The crystals were collected by filtration and dried under a stream of air.

NONCRYSTALLINE FORM was prepared by Lyophilization [3] and Spray drying [4].

CHARACTERIZATION OF VARIOUS FORMS :

X-RAY POWDER DIFFRACTION patterns were obtained with Philips Diffractometer PM 9920/05 using Ni filtered Cu K alfa radiations at a scan rate of 6.000 deg/min.from 5^{o} to 60^{o}.

INFRA RED SPECTRA were recorded as KBr pellets using IR Spectophotometer (FTIR NICOLET 5DX) from 4000-600 /cm.

D.T.A & T.G.A. was performed using RIGAKU 8150 Thermal Analyser.

POLARISING MICROSCOPY was done using CARL ZEISS Pol. microscope.

SCANNING ELECTRON PHOTOMICROGRAPHS were obtained using JSM840 SEM (Jeol make) scanning electron microscope. Solid samples were coated with thin gold film by SPUTTERING TECHNIQUE and scanned at 5KV.

ULTRA VIOLET SPECTRA of aqueous solutions were recorded in the near UV region from 190-400 nm using SHIMADZU UV 2000.

NUMBER OF SOLVENT MOLECULES [5,6] was determined by measuring the absorbance of aqueous solutions of various crystalline forms($2.78*10^{-3}M$).

HYGROSCOPICITY : Samples (1gm.) of various forms were stored in saturated salt solutions of various relative humidity (R.H.) in dessicators (0-98%) at $25\pm0.5^{o}C$ for 3 weeks. Change in water content was determined by measuring the weight.

TABLE-I

Crystallisation data

SOLVENT	CRYSTAL FORM	CRYSTALLISATION TIME (hr)	CRYSTALLISATION CONDITION	DENSITY (gm/cc) IN ACETONE	IN DIOXANE
ETHANOL	FORM I	6-24	Cool Evaporation	0.8300	0.8425
ISOPROPANOL	FORM II	6-12	Cool Evaporation	1.5460	1.5660
METHANOL	FORM III	6-12	Cool Evaporation	1.3150	1.3090
WATER	FORM IV	24 days	Evaporation	1.1656	1.1621

EQUILIBRIUM SOLUBILITY (7)of various samples was measured at 313 nm at 20, 25, 30, 32.5, 35, 37.5, 40 and 50°C.

DENSITY of various samples was measured by Liquid displacement method at 25±0.5°C using acetone and dioxane.

STABILITY STUDIES

1.STABILITY AGAINST MOISTURE : Effect of moisture on solid state stabilty and polymorphic stability of various forms stored under various R.H.(0-98%) at 25±0.5°C was investigated by analysing samples at appropriate intervals using UV spectrophotometry, HPLC and D.T.A.-T.G.A.

2.STABILITY AGAINST TEMPERATURE : Effect of temperature on solid state stability and polymorphic stability of various forms stored in dessicators at 25±0.5°C, 40±0.5°C and 65±0.5°C was investigated by analysing samples at appropriate intervals using UV spectrophotometry and D.T.A.-T.G.A.

3.STABILITY AGAINST COMPRESSION FORCE :500mg of each sample was compressed using Hydraulic press at 4, 5 and 6 Tons of pressure and screened for polmorphic changes by X-RD and D.T.A.-T.G.A.

RESULT AND DISCUSSION

Conditions during crystallisation of various forms are given in Table-I.

CHARACTERIZATION OF VARIOUS FORMS :

X-RD patterns of various forms are shown in Fig.1. The pattern is characteristic of each form and can be used for identification.

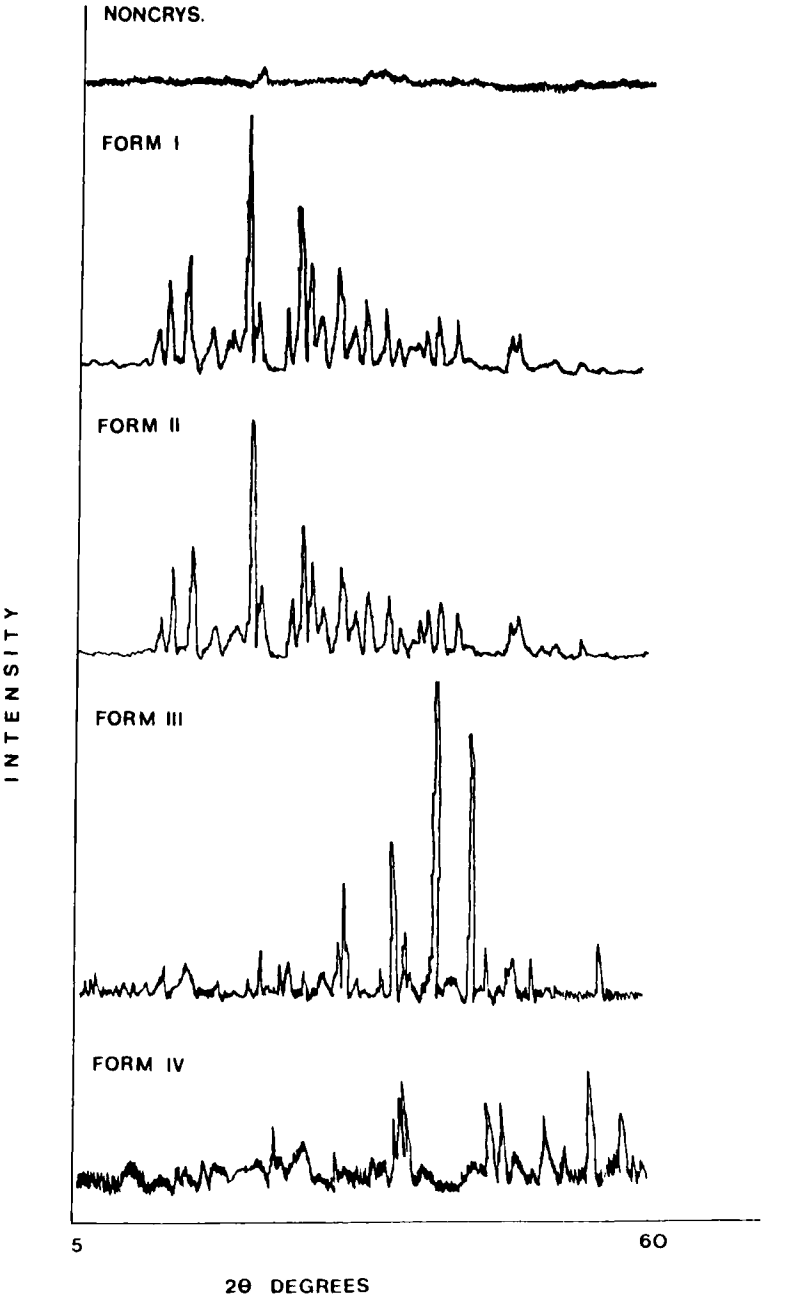


FIG. 1

X-Ray powder diffraction patterns of various forms of RANITIDINE-HCl.

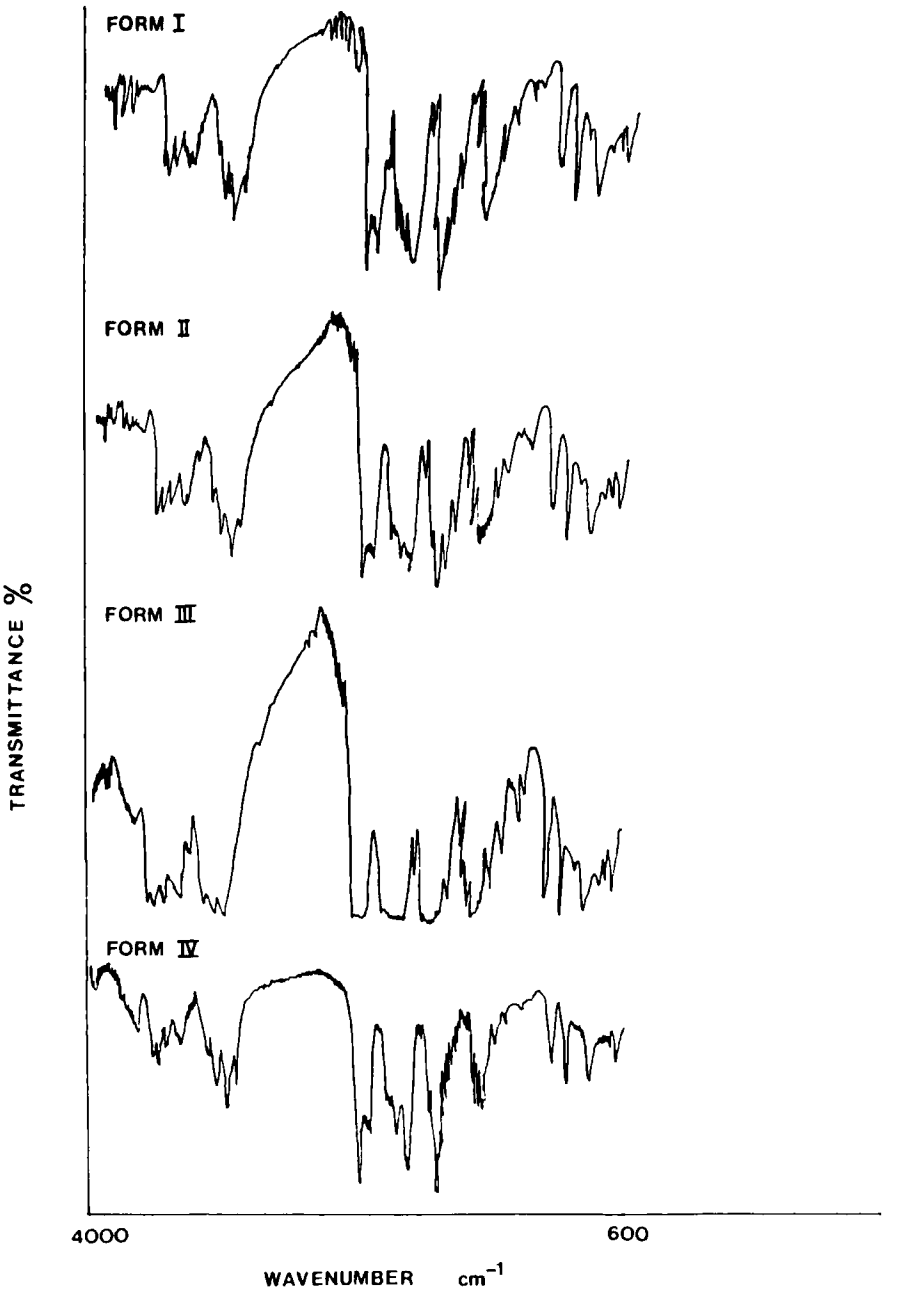


FIG. 2
Infra red spectra of various forms of RANITIDINE-HCl.

TABLE-II

Infrared spectral data

PEAKS /cm	FORM I % T	FORM II % T	FORM III % T	FORM IV % T
3415	61.20	19.50	38.20	51.40
3272	60.00	6.30	20.40	33.70
3116	55.20	6.30	21.60	36.10
2635	50.21	6.10	15.60	29.60
2586	46.78	6.00	13.20	26.00
1618	31.16	5.83	7.90	16.90
1384	35.56	5.83	7.90	18.70
1228	29.21	5.83	6.70	13.90
1032	46.50	6.30	14.40	32.10
748	57.60	7.33	22.80	42.90
719	50.21	6.08	18.00	35.70
676	52.80	6.30	19.20	38.10

No definite peaks were apparent in the pattern of noncrystalline form.

IR SPECTRA of various forms is different and indicates differences in crystal structure (Fig.2). Characteristic peaks with % T of various forms are given in Table-II.

The thermographs obtained by D.T.A.-T.G.A. are shown in Fig.3. and data is given in Table-III. All the polymorphic forms had different melting and decomposition points. Noncrystalline form has lowest melting point (119.0°C). With least delta Hf (Enthalpy of Fusion), FORM I requires least energy to lose its crystal structure and hence shows greatest solubility among the crystalline forms. Weight loss % in T.G.A. was maximum in FORM IV (29.536%). High weight loss in FORM IV indicates solvate formation.

Polarising photomicrographs of various forms are shown in Fig.4. All the crystalline forms were ANISOTROPIC and BIAXIAL and hence belong to ORTHORHOMBIC, MONOCLINIC or TRICLINIC crystal systems. Fig.5. showing Scanning electron photomicrographs of various

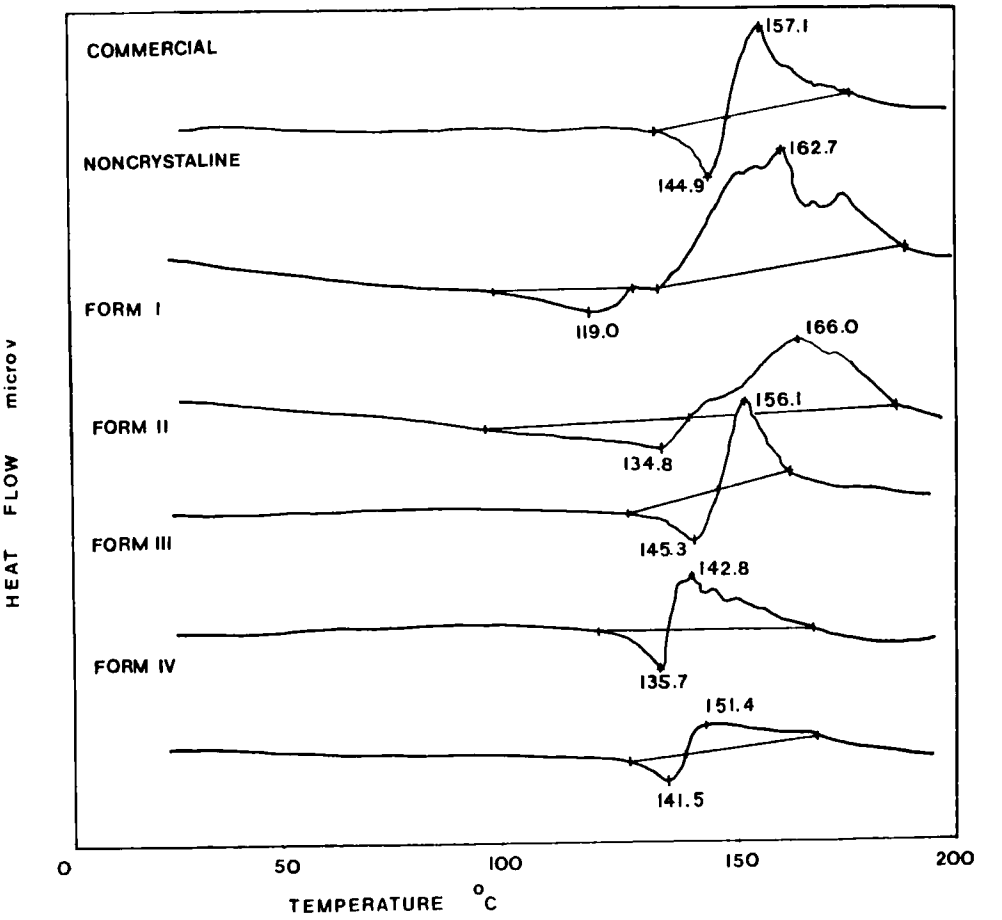


FIG. 3

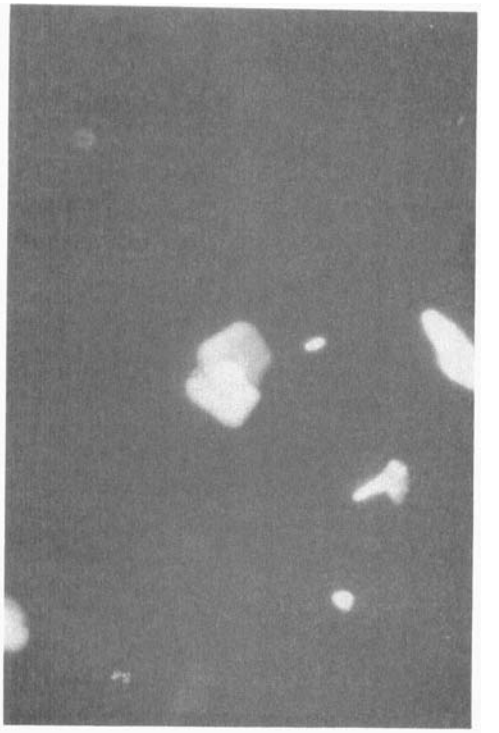
D.T.A. & T.G.A. of various forms of RANITIDINE-HCl.

TABLE-III

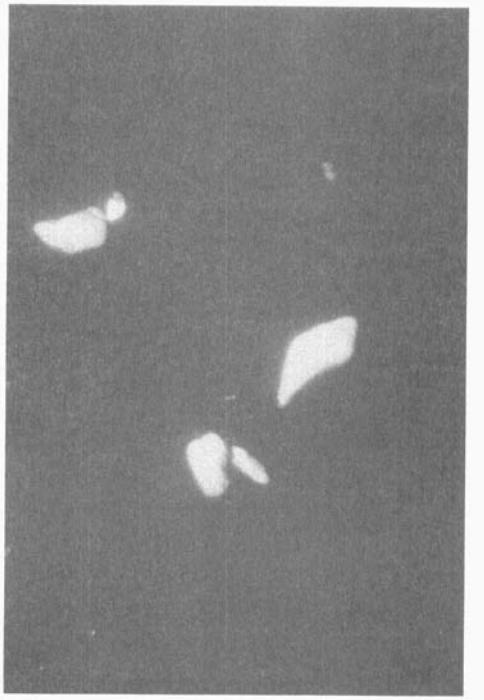
D.T.A. & T.G.A. data

SAMPLE	M.Pt. °C	Δ Hf muv.min/g	Decomp.Pt. °C	Δ Hd muv.min/g	Weight Loss %
COMMERCIAL	144.9	1188.72	157.1	2456.85	14.275
NONCRYS.	119.0	0459.10	162.7	2048.96	11.764
FORM I	134.8	0473.10	166.0	2146.30	11.327
FORM II	145.3	0740.50	156.7	1258.33	13.317
FORM III	135.7	0536.45	142.8	2887.06	15.649
FORM IV	141.5	0620.74	151.4	1551.57	29.536

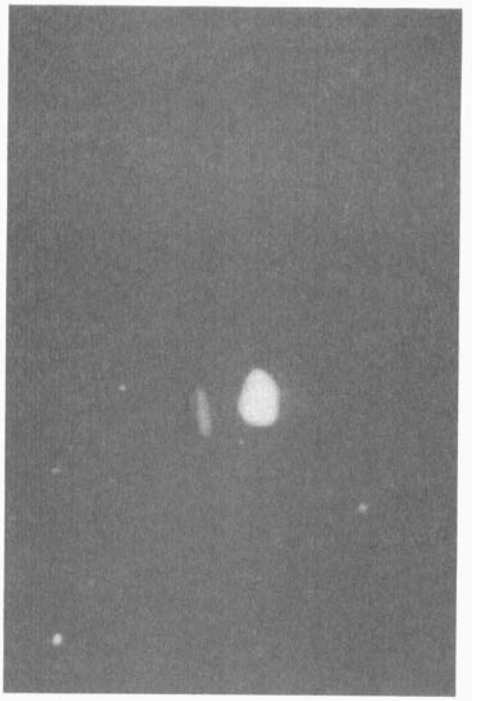
FORM I



FORM II



FORM III



FORM IV

FIG. 4

Polarising photomicrographs of various forms of RANITIDINE-HCl.

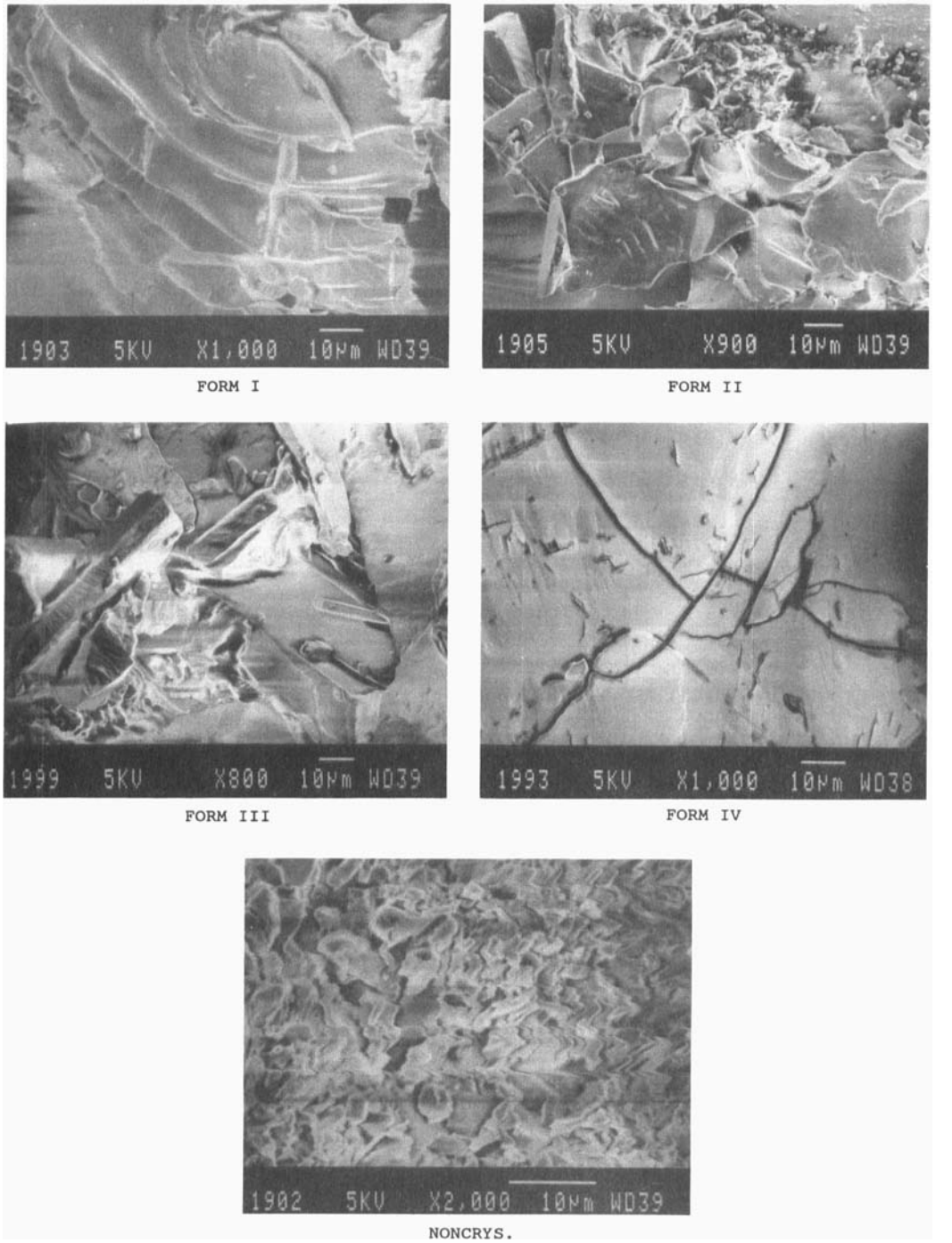


FIG. 5

Scanning electron photomicrographs of various forms of RANITIDINE-HCl.

TABLE-IV

No. of solvent molecules in various crystal forms

SAMPLE	Absorbance of 2.78×10^{-3} M soln.	Calculated Absorbance for Equimolar soln. of crystals	No. of solvent mol/ drug mol.
NONCRYS.	0.497	-	-
FORM I	0.446	0.439	1
FORM II	0.463	0.457	1/2
FORM III	0.453	0.455	1
FORM IV	0.472	0.472	1

forms reveals distinct differences in surface characterstic of solids. Noncrystalline form shows a distorted surface. FORM I shows repeated contact twinning of crystals with a pinacoidal cleavage resulting in a step like surface. FORM II and FORM III exhibit orthorombic crystals. Crystals of FORM IV were platy in habit.

UV spectra of various forms was recorded and data is given in Table-IV. Aqueous solutions of various forms had different absorbance at same max. values. This observation was utilised in detrmination of number of solvent molecules. All the forms obtained were partial or complete solvates and hence, Pseudopolymorphs.

The increase in water content was maximum in noncrystalline form and minimum in FORM II. Various crystalline forms in increasing order of Hygroscopicity are :

FORM II < FORM I < FORM IV < FORM III

Fig.6. shows the increase in moisture content vs R.H. at $25 \pm 0.5^{\circ}C$ and data is tabulated in Table-V.

Results of equilibrium solubility measurement (Fig.7.) show that solubility of noncrystalline forms was higher than the crystalline forms. Crystalline forms in increasing order of solubility at $25 \pm 0.5^{\circ}C$ are :

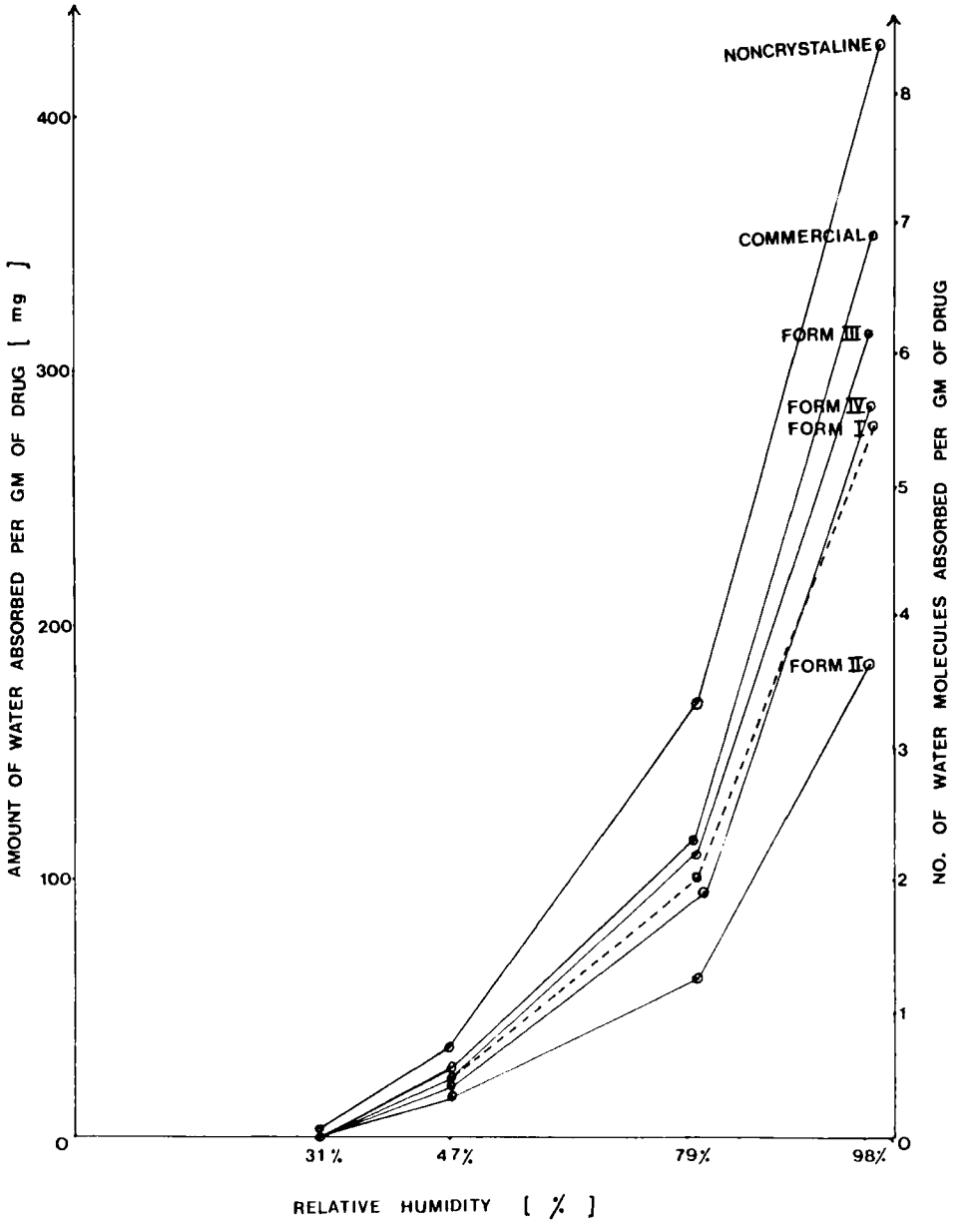


FIG. 6
Increase in moisture content of various forms at different R.H.

TABLE-V

Hygroscopicity data

SAMPLE	Amount of moisture absorbed in mg.	No. of water molecules/ drug molecule.
COMMERCIAL	353.0	6.90
NONCRYS.	428.0	8.39
FORM I	279.0	5.47
FORM II	184.0	3.60
FORM III	313.0	6.13
FORM IV	285.0	5.58

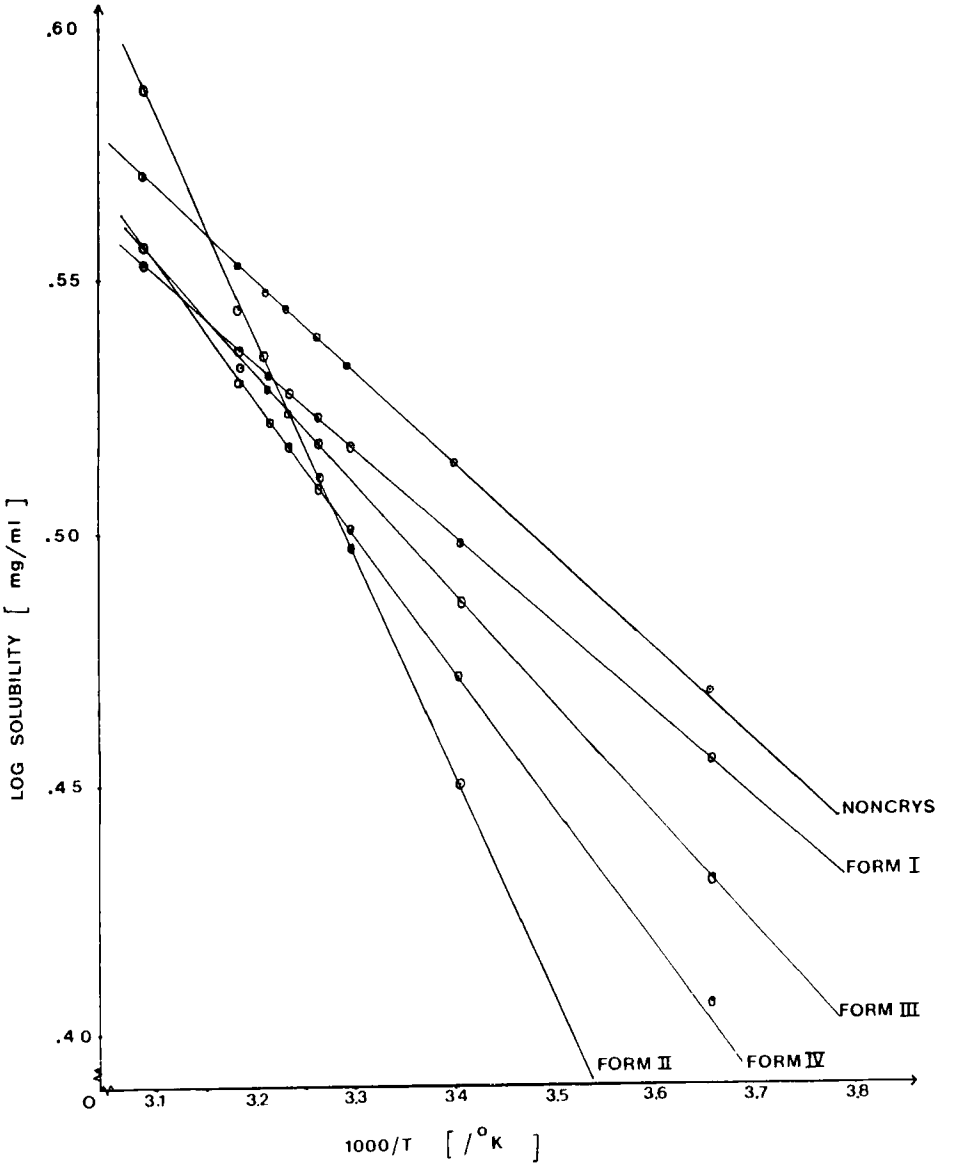


FIG. 7

Equilibrium solubilities of various forms at different temperatures.

TABLE-VI

Solubility data

FORMS	TRANSITION TEMPERATURE (°C)	GIBB'S FREE ENERGY (Δ G)
I to II	37.5	-152.770
I to III	42.4	-013.685
I to IV	45.9	-028.253
III to II	35.0	-121.234
III to IV	50.0	-014.567
IV to II	33.2	-087.690

TABLE-VII

D.T.A. & T.G.A. data of Stability against moisture

SAMPLES	INITIAL		31% R.H.		47% R.H.	
	M.Pt.°C	Wt. loss%	M.Pt.°C	Wt. loss%	M.Pt.°C	Wt. loss%
COMMERCIAL	144.9	14.275	147.0	09.847	144.0	27.918
NONCRYS.	119.0	11.764	145.1	22.648	144.2	21.135
FORM I	134.8	11.327	139.5	12.385	140.7	21.787
FORM II	145.3	13.317	142.8	09.028	143.9	10.001
FORM III	135.7	15.649	139.5	10.068	140.1	10.667
FORM IV	141.5	29.536	140.1	12.136	140.2	12.557

FORM II < FORM IV < FORM III < FORM I

The transition temperatures and Gibbs free energy (Δ G) obtained from solubility curves are given in Table-VI.

Results of density measurement are given in Table-I. Noncrystalline form has the lowest density which indicates lack of ordered arrangement. Crystalline forms in increasing order of densities at 25±0.5°C are :

FORM I < FORM IV < FORM III < FORM II

STABILITY STUDIES :

1. STABILITY AGAINST MOISTURE : Results of UV and HPLC analysis of samples show that all the forms decompose above 47% R.H. Results of D.T.A.-T.G.A. (Table-VII) exhibit changes in melting

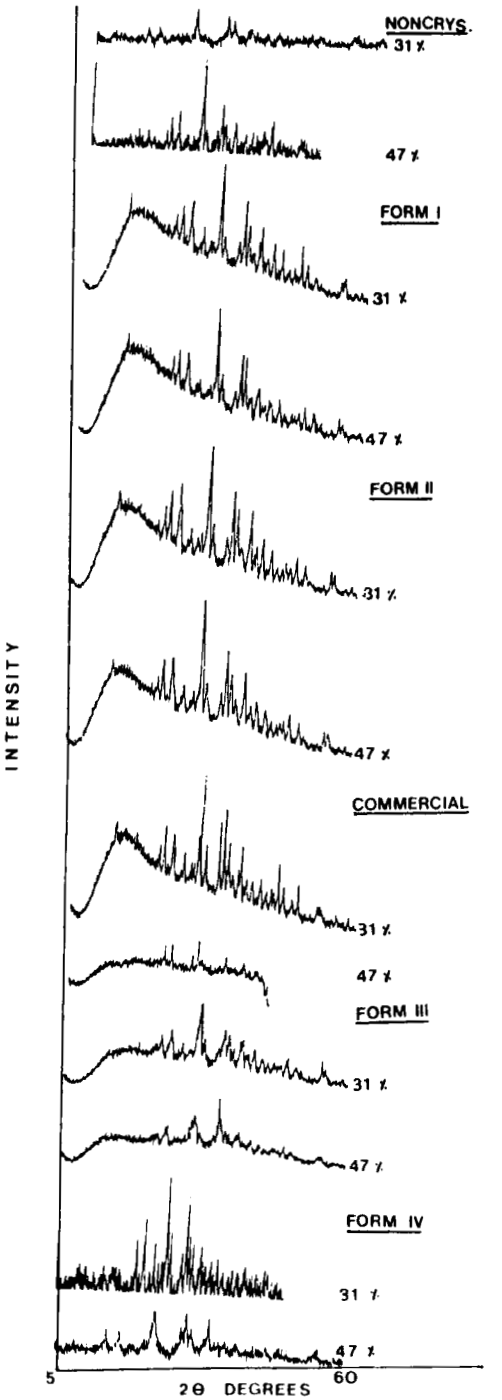


FIG. 8

X-Ray diffraction patterns of various forms at different R.H.

TABLE-VIII

D.T.A. & T.G.A. data of Stability against temperature

SAMPLES	INITIAL		25 °C		40 °C		65 °C	
	M.Pt.°C	Wt.loss%	M.Pt.°C	Wt.loss%	M.Pt.°C	Wt.loss%	M.Pt.°C	Wt.loss
COMMERCIAL	144.9	14.275	145.7	12.028	147.3	09.875	132.4	11.756
NONCRYS.	119.0	11.764	139.7	11.364	146.1	15.728	136.0	05.662
FORM I	134.8	11.327	135.2	12.609	141.6	09.762	140.1	13.870
FORM II	145.3	13.317	144.9	13.068	144.8	09.710	137.6	09.828
FORM III	135.7	15.644	136.3	15.662	144.2	11.023	142.0	14.072
FORM IV	141.5	29.536	143.9	21.787	146.1	15.829	140.7	10.001

points of all the samples except FORM II. X-RD patterns of various samples (Fig.8.) indicates changes in the polymorphic forms. Apparent peaks in the pattern of noncrystalline form suggest its transformation to crystalline state. FORM II retains its crystal structure. All other forms exhibit loss in crystallinity on absorption of moisture.Various crystalline forms in increasing order of stability are :

FORM III < FORM IV < FORM I < FORM II

2. STABILITY AGAINST TEMPERATURE : Samples stored at 40±0.5°C and 65±0.5°C grew darker in colour and formed a coherent mass. Results of D.T.A.-T.G.A. (Table-VIII) show rise in melting point of noncrystalline form. This suggests its transformation to crystalline state. Depression in melting points was observed in samples kept at 65°C for 3 weeks. Various crystalline forms in increasing order of stability are :

FORM III < FORM IV < FORM I < FORM II

3.STABILITY AGAINST COMPRESSION FORCE :Fig.9. shows X-RD patterns of samples on compression at 4, 5 and 6 Tons of pressure. On increasing the force of compression peaks characteristic of crystalline structure appeared in the pattern of noncrystalline form. This suggests that on compaction and consolidation, fusion

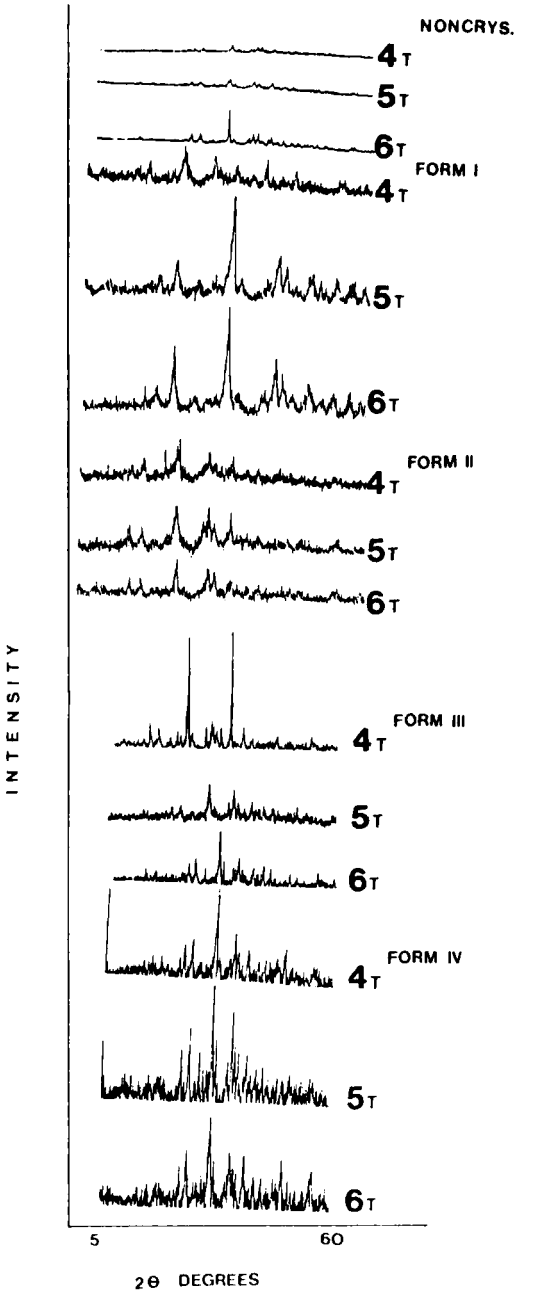


FIG. 9

X-Ray diffraction patterns of various forms after compression at 4, 5 and 6 tons.

TABLE-IX

D.T.A. data of Stability against Compression force

SAMPLES	MAGNITUDE OF COMPRESSION FORCE APPLIED			
	0 TONS M.Pt.°C	4 TONS M.Pt.°C	5 TONS M.Pt.°C	6 TONS M.Pt.°C
NONCRYS.	119.0	143.1	143.5	147.1
FORM I	134.8	141.3	143.8	144.9
FORM II	145.3	142.7	140.1	142.0
FORM III	135.7	146.1	144.5	145.9
FORM IV	141.5	143.9	148.9	142.6

of particles takes place that results in developement of crystalline form. In FORM I peak at 21.030 increased with increase in compression force. In FORM II peak at 25.960 diminished with increase in compression force. FORM III and FORM IV show structural deformation on compaction. Results of D.T.A.-T.G.A.(Table-IX) show an increase in melting points of various forms with increase in applied force suggest conversions to the stable state.

CONCLUSION

A.The crystal forms obtained were pseudopolymorphs. FORM I, II and III are solvates of Ethanol, Isopropanol and Methanol respectively and FORM IV is a monohydrate.

B.FORM II is the most stable crystalline form and all the other forms convert to FORM II during storage.

C.**HUMIDITY, TEMPERATURE & COMPRESSION FORCE** affect the chemical as well as polymorphic stability of various forms.

D.Transition temperatures for various forms fall in the range of 37.5°C. So, the storage of drug at R.H. less than 31% and at a

temperature less than 25°C ensures the polymorphic stability of the drug.

REFERENCES

1. H.J.Ruoff et al, Gastroenterology, 76, 1230/1979.

2. D.L.Crookes (Glaxo), C.A. 97, 61014g/1982.

3. J.Haleblian, R.Koa & J.Biles, J.Pharm. Sci. 60, 1485/1971.

4. Albert S. Rankell, Theory and practice of Ind. Pharm.60/1987.

5. M.A.Moustafa et al, J. Pharm. Sci.63, 1103/1974.

6. E. Sheffer & T. Higuchi, J.Pharm. Sci. 52, 781/1963.

7. J.C.Boylan, Theory and Practice of Ind. Pharm. 457/1987.