DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(15), 2749-2769 (1987)

EFFECT OF CRYSTALLINITY ON ABSORPTION AND EXCRETION PATTERNS OF IBUPROFEN, TINIDAZOLE AND LORAZEPAM

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ABSTRACT

Various physical forms of Ibuprofen, Tinidazole and Lorazepam were prepared. Different crystal forms of these drugs were characterized with the help of Differential Scanning Calorimetry X-ray diffrection patterns, I.R. spectra and micro photographs of samples. The dissolution and diffusion rates of physical forms were determined. The absorption pattern of drug by insitu rat intestine was also studied using Doluisio technique. After oral administration cumulative amount of drug excreted in urine was determined.

INTRODUCTION

Different polymorphs have difference in hydrogen bonding, dissolution rate, density, melting point, stability and packing energy.[1,2] As polymorphs are distinct forms having different lattice structure, they give rise to distinguishable X-Ray diffraction, D.S.C. patterns and I.R. spectra.[3,4] Infrared spectra is helpful to characterize solvates and polymorphs. The X-Ray diffraction pattern is helpful in determining the crystallinity, molecular structure, positions of atoms in the molecule of drugs and for distinguishing different polymorphs of the drugs. Optical microscopy is useful to find out the morphological character of the drug particle and the particle size. Differential scanning calorimetry can be used to determine the phase transition stability kinetics of different crystal forms, polymorphism and drug compatability with excipients.

Poorly water soluble drugs may have more bioavailability problems. Particle size reduction may be attempted to overcome above problems. The

degree of crystallinity of drug may be changed by the suitable choice of solvents. During micro-precipitation or particles size reduction by milling lattice defects may be created at the crystal surface, which may affect the stability pattern. The kinetic behaviour of the drug particles are controlled by the crystallinity, density, hygroscopicity, surface character, melting point, extent of solvation, polymorphic transfer and phase change.

Rastogi et al[5] correlated the reaction rate of solids with void volume, density, shape and size of the particle and examined the geometric implications of diffusion behaviour of solids. Crystalline compounds are more stable than glass or amorphous form. Stable polymorph posess lower free energy, higher melting point, greater chemical stability whereas metastable form has higher solubility and dissolution rates.

The molecular structure and crystal nature of ethanol adduct of lorazepam was studied by Bandoli and Clements.[6] The adduct consists of an ethanol and lorazepam molecules linked together by hydrogen bonds. The determination of particle

size, shape, melting point, study of U.V. and I.R. spectra, dissolution and diffusion studies of various physical forms of drugs were undertaken by Udupa et al.[7] The present work is undertaken to investigate the effect of crystallinity of Ibuprofen, Tinidazole and Lorazepam on their absorption and excretion patterns.

MATERIAL AND METHOD

Ibuprofen B.P., Tinidazole (Standard Organics, Hyderabad), Lorazepam (Themis Chemicals, Bombay), Distilled Ethanol, P.E.G. 4000 and Propylene glycol (M/s. S.D. Fine Chemicals, Bombay), Polyvinyl pyrrolidone (M/s Loba Chemie), Chloroform and Acetone A.R. (M/s B.D.H.).

Preparation of supercooled variety of drug by shock cooling

1 gm. of each drug was heated carefully over a hot plate in glass beaker, with constant stirring to prevent charring. The melt was spread quickly over a stainless steel plate kept over water bath filled with ice. The solidified material was scrapped with the aid of a S.S.

spatula ground and passed through 80 mesh. The samples were labelled as 1 a., 2a and 3a.

Preparation of slow cooled variety of drug

1 gm. of each drug was melted as described in previous section, the melt was transferred to a hot air oven maintained at 105°C. The oven was switched off and the temperature was allowed to fall. The sample was removed when oven reached the room temperature, ground and passed through 80 mesh. These samples were labelled as 1b, 2b and 3b.

Preparation of various physical forms of drugs Precipitated from ethanol, chloroform, propylene glycol and acetone

1 gm. of each drug was dissolved separately in 50 ml. each of slightly warmed solvent. Each solution, was filtered through Whatman No. 4 Filter Paper and the filtrate was slowly added to 500 ml. of ice cold water around 5°C in a beaker with stirring. After allowing the precipitate to settle for half an hour, it was separated by filtration through a Whatman No. 4 Filter Paper

and the samples were stored in a desiccator. The samples were lebelled as (Ibuprofen) 1c, 1d, 1e and 1f, (Tinidazole) 2c, 2d, 2e and 2f, (Lorazepam) 3c, 3d, 3e and 3f respectively.

Evaluation of various Physicochemical Properties

The everage particle size and shape of the physical form was determined by taking the photo-micrographs using Zeiss Photomicroscope. X-Ray Diffraction pattern of samples were obtained using Philips P.W. 1010 X-Ray diffractometer with Co.K-alpha radiation and Ni filter. From 2Ø values, d values were calculated using Bragg's equation, $n\lambda = 2\ d.\ \sin Ø$. Study of Differential scanning calorimetry of samples was undertaken using Perkin Elmer D.S.C. Unit.

Absorption Study

Insitu absorption study of various polymorphs was conducted in Rat Intestine by Doluisio Technique.[8] 20 mg. of Ibuprofen Powder, 50 mg. Tinidazole Powder and 100 mg. Lorazepam Powder were dissolved in 100 ml each of pH 7.4 buffer. 0.2 ml of samples were drawn every 15 mins. for estimating the concentration of drug in

the intestinal fluid. The difference in concentration representing the amount of drug absorbed is calculated. For analysis of drugs spectrophotometric methods were employed.[7]

Excretion Study

Seven healthy human volunteers in the age group of 30-35 years having 55-60 kg. body weight were selected. 400 mg of each crystal form of Ibuprofen and 4 mg of Lorazepam were separately filled in capsules and administered orally along with 200 ml of water to human volunteers in a non randamized cross over study. 10 ml of urine samples excreted at each intervals were numbered and preserved for analysis. After collection of urine at each interval the volunteer was asked to drink 200 ml of water. The amount of urine excreted at each interval was messured and recorded. The urine samples were collected upto 8 hours after oral administration of Ibuprofen or Lorazepam. The experiment was repeated in the same seven volunteers, after 2 weeks wash out period.

After extraction of Ibuprofen from the urine sample, it was treated with 0.5% w/v aqueous solution of safranin and coloured complex was

extracted with chloroform. The absorbance of colour was measured at 570 nm.[9,10] Cumulative amount of Ibuprofen excreted upto 8 hours was calculated.

Lorazepam excreted in urine was estimated spectrofluorometrically,[11] by activating the samples at 402 nm and taking fluorescence readings at 448 nm in a Amino Bowman spectrofluorometer.

RESULTS AND DISCUSSION

Solvents with high surface tension and dielectric constant values and low specific gravity (acetone, ethanol and propylene glycol) gave smaller particles. The physical form of Ibuprofen, Tinidazole and Lorazepam precipitated from propylene glycol and acetone had low particle size and had higher diffusion coefficient, absorption and excretion rates (Table 1, 2 and 3). The X.R.D. patterns, microphotographs, I.R. spectra and D.S.C. pattern of various physical forms differ from each other indicating the polymorphism.

The diffusion rates of irregular and tubular forms are lower but the circular shaped physical

TABLE 1 : PHYSICAL FORMS OF IBUPROFEN AND THEIR ABSORPTION & EXCRETION PATTERN

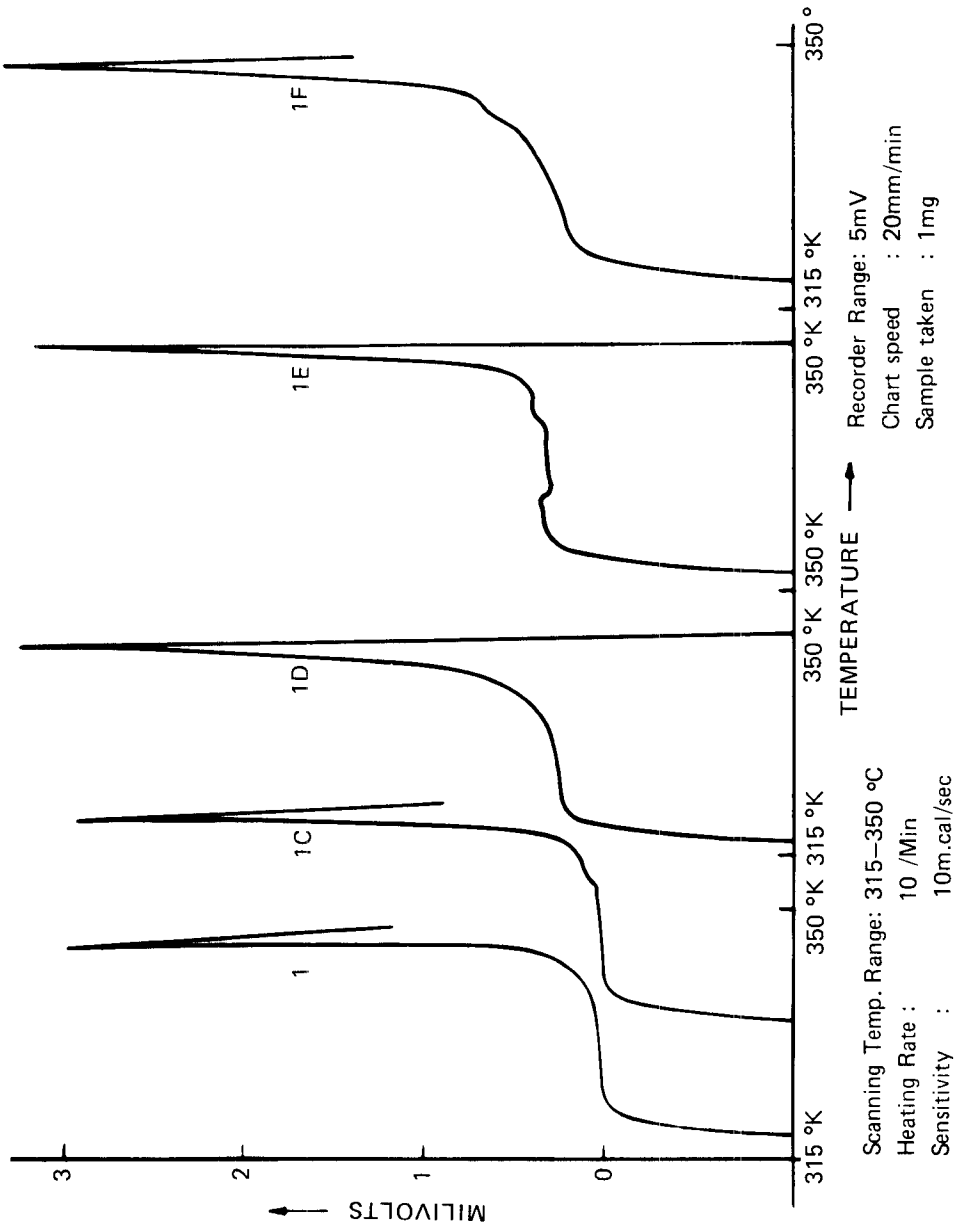
Sample No.	Physical Form	Particle size (Microns)	Absorption half life $t_{\frac{1}{2}}$ Mins. (Av of 3)	Absorption rate constant Ka min^{-1} (Av of 3)	Cum. mg. drug excreted in 8 hours (Av of 3)	S.D.±
1.	Control Sample	6-15	88.85	0.0078	5.4	0.6557
1c.	PPT from ethanol	3-15	64.77	0.0107	5.8	0.6708
1d.	PPT from Chloroform	10-20	123.76	0.0056	2.3	0.6800
1e.	PPT from Propylene glycol	2-6	50.69	0.0137	6.3	0.8062
1f.	PPT from Acetone	3-10	62.51	0.0111	6.1	0.7012

TABLE 2 : PHYSICAL FORMS OF TINIDAZOLE AND THEIR ABSORPTION PATTERNS

Sample No.	Physical Form	Particles Size (Microns)	Absorption half-life $t_{\frac{1}{2}}$ Mins (Av. of 3)	Absorption Rate constant Ka Min^{-1} (Av. of 3)
2.	Control sample	30-120	42.18	0.0164
2a.	Supercooled Form	5-20	20.38	0.0340
2c.	PPT From Ethanol	L 30-120 W 15-20	72.41	0.0096
2d.	PPT From Chloroform	L 40-120 W 6-12	45·00	0.0154
2e.	PPT From Propylene glycol	L 20-50 W 3-6	9.02	0.0768
2f.	PPT From Acetone	L 30-100 W 15-20	68.22	0.0102

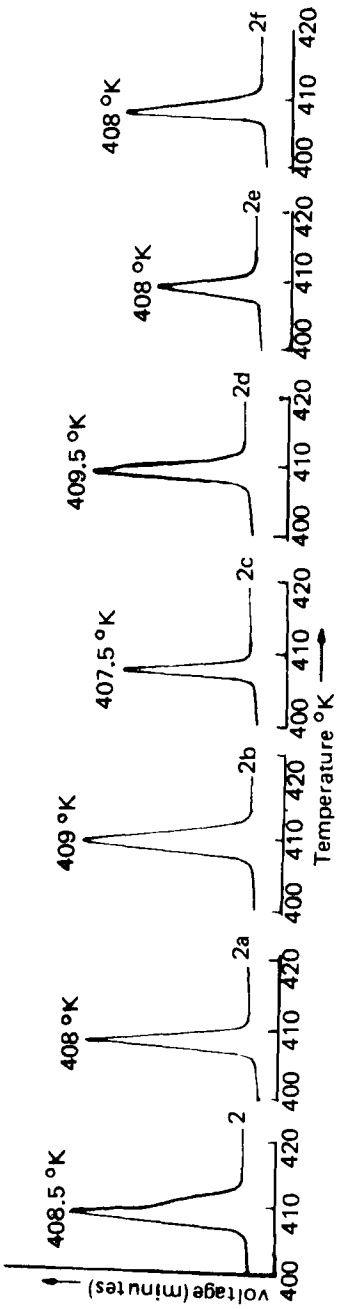
TABLE 3 : PHYSICAL FORMS OF LORAZEPAM AND THEIR ABSORPTION & EXCRETION PATTERN

Sample No.	Physical Form	Particles Size (Microns)	Absorption halflife $t_{\frac{1}{2}}$ min (Av. of 3)	Absorption Rate constant Ka, min^{-1} (Av. of 3)	Cum. Drug Excreted in 6 hours (Nanograms)	S.D.±
3.	Control Sample	3-15	8.87	0.0781	567	30.6
3c.	PPT From Ethanol	L 15-75 W 5-10	11.15	0.0621	267	55.3
3d.	PPT From Chloroform	L 15-35 W 2-4	18.83	0.0368	200	25.5
3e.	PPT From Propylene glycol	2-6	4.45	0.1556	837	45.3
3f.	PPT From Acetone	10-15	7.17	0.0966	720	72.1

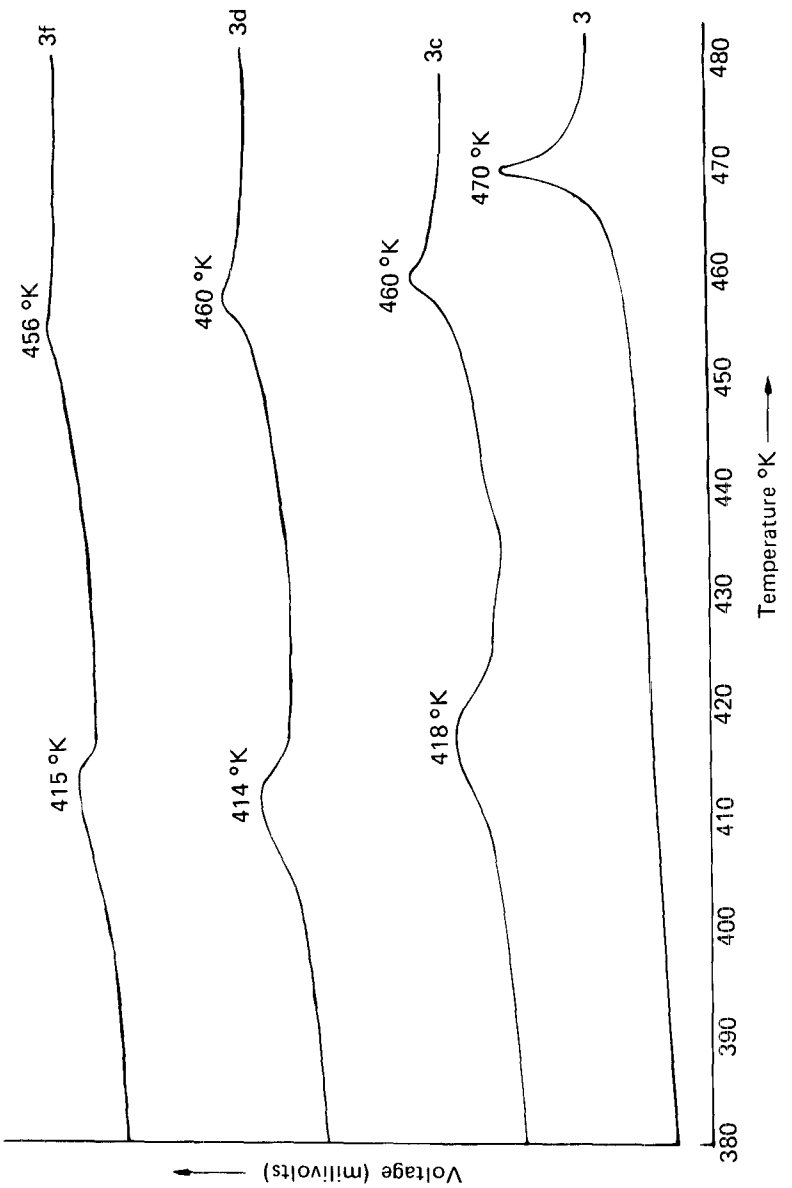


1 DIFFERENTIAL SCANNING CALORIMETRY (D.S.C.):IBUPROFEN

Instrument used: PERKIN ELMER D.S.C. Unit

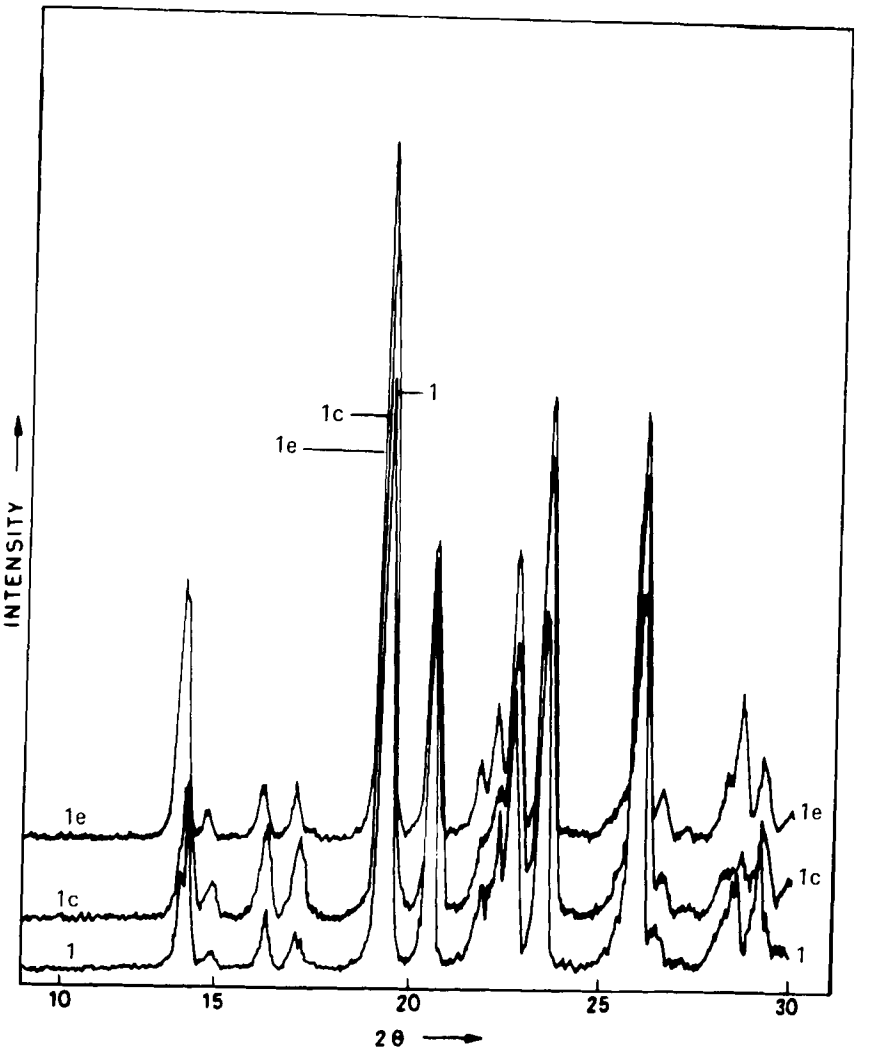


2 DIFFERENTIAL SCANNING OF TINIDAZOLE (Instrument Used : Perkin Elmer D.S.C. – 1 Unit)
Scanning Temp. Range = 400 °K – 420420 °K
Heating Rate = 10 K/min
Sensitivity Range = 2M. Cal/sec.,50mv
Chart speed = 40mm/min

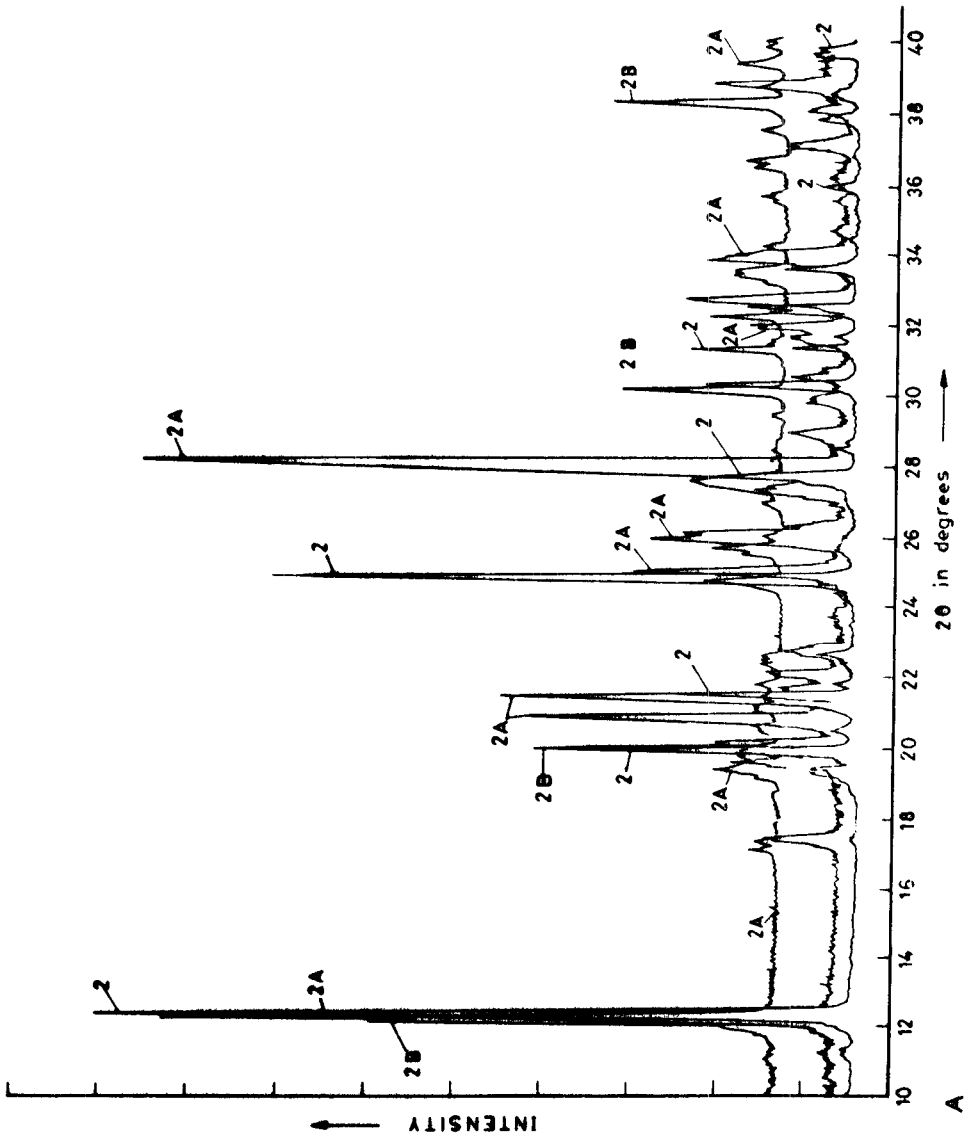


3 DIFFERENTIAL SCANNING CALORIMETRY OF LORAZEPAM (Insrtument Used: Perkin Elmer D.S.C.-1Unit).

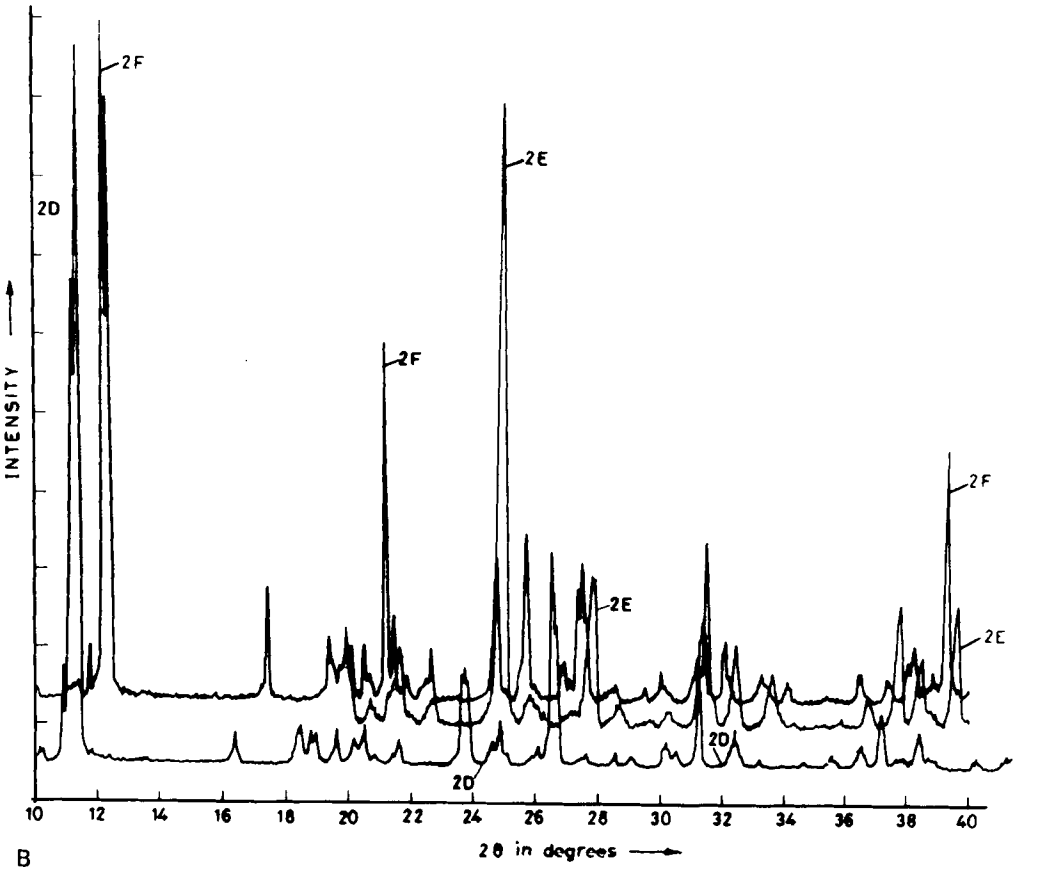
Scanning Temp. Range : 380 °K - 480 °K
Heating Rate = 10 K/min
Sensitivity Range = 2M. Cal/sec.,50mV
Chart speed = 40mm/min



4 X-RAY DIFFRACTION PATTERNS OF IBUPROFEN SAMPLES
2°/mt., 1°/cm, CoKα, λ = 1.7902 Å

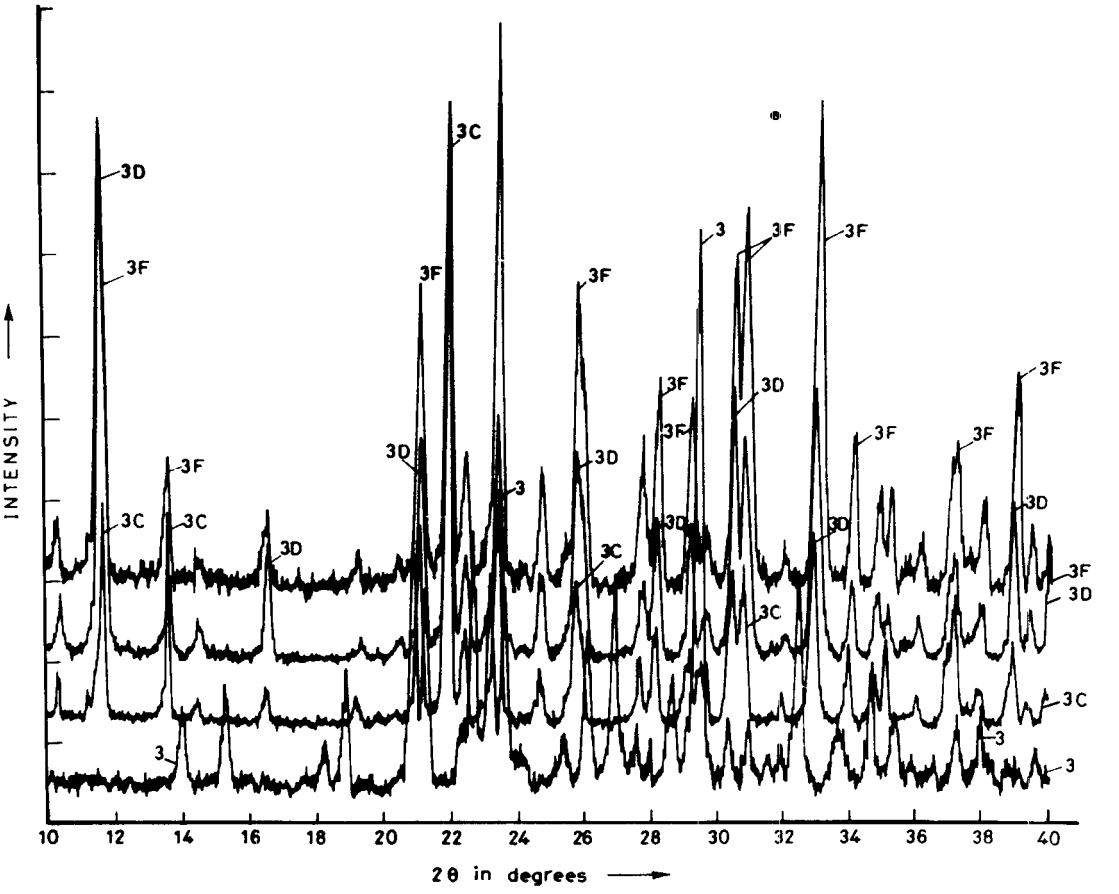


5A. X - Ray Diffraction Patterns TINIDAZOLE SAMPLES
Radiation : Co. K_α , λ = 1.7902 °A , 1°/cm , 2°/minute



5B. X-Ray Diffraction Patterns of TINIDAZOLE SAMPLES
Radiation : CuK_{α} , λ = 1.7902°A, 1°/cm, 2°/minute

form (precipitated from propylene glycol) exhibited higher diffusion rate. The particle size, shape, crystallinity of various physical forms influence dissolution, diffusion, absorption and excretion rates (Tables 1, 2, and 3) of drugs.



6 X-Ray Diffraction Patterns of LORAZEPAM SAMPLES
Radiation : Co. K_{α} , λ = 1.7902 °A, 1°/cm, 2°/minute

The different melting points and nature of exothermic peaks of various physical forms of Ibuprofen, Tinidazole and Lorazepam are evident from the D.S.C. scanning (Fig. 1, 2 and 3). Different crystal forms of drugs are also characterized by the X-Ray diffraction pattern. The change

in d value (interplanar distance) indicates different arrangement of molecule in polymorphs of drugs (Fig. 4, 5 and 6).

The additional X-Ray diffraction peaks were observed in the monoclinic crystalline solvates of Lorazepam (Fig. 6). In the D.S.C. curves of Lorazepam solvates two exothermic peaks were observed whereas Lorazepam standard sample had only one exothermic peak (Fig. 3). The solvate is a adduct of solvent used in crystallization and the drug Lorazepam. The nature of D.S.C. curves of different physical forms of Ibuprofen also varied to some extent (Fig. 1). The exothermic peaks of Tinidazole physical forms did not differ much (Fig. 2). But the melting points of Tinidazole polymorphs were different.

CONCLUSION

By modification of crystal forms of poorly water soluble drugs like Ibuprofen, Tinidazole and Lorazepam by precipitation from suitable solvent, it is possible to alter the diffusion, absorption and excretion rates.

ACKNOWLEDGEMENT

The authors are thankful to Dr. G. Jagdeesh, Department of Pharmaceutics, B.H.U. for helping to set up the experiment on absorption study in rat intestine, to Dr. Surolia, Dr. Shastri, Mr. Sanjeev Mathur and Mr. L. Ganapathy of Indian Institute of Sciences, Bangalore for helping in X.R.D. and D.S.C. experiments.

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