*Acta Pharmaceutica Turcica*
*44:105-118 (2002)*

# Improvement of Dissolution Rate and Aqueous Solubility of Nitrazepam By Solid Dispersion Technique

**S. Singh[1*], A. A. H. Sathali[2] and S. B. Jayaswal[2]**

[1]Department of Pharmacology, Motilal Nehru Medical College, Allahabad, INDIA.[2]Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi, INDIA.

## ABSTRACT

The aqueous solubility and dissolution rate of nitrazepam were increased using solid dispersion technique. The solvent fusion and coprecipitation methods were employed (with different solvents) to prepare the solid dispersion with polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) polymers of different molecular weights. The solid dispersions were evaluated for drug content and dissolution rate. The dissolution rates were affected by the solvent used, molecular weight of the polymer, drug: polymer ratio and the technique employed. The solid dispersion with PVP 44000, solvent chloroform and drug: polymer ratio 1:19 (Batch $L_1$) displayed maximum aqueous solubility and the best dissolution rate. Studies showed a change in the physical state of the drug from crystalline to amorphous form in solid dispersion. The tablet prepared with Batch $L_1$ showed drug released in nearly zero-order fashion in comparison to the marketed product. The stability studies carried out at three different temperatures showed no change in the drug content of the prepared tablets.

**Key Words:** Nitrazepam; solid dispersion; aqueous solubility; dissolution rate; tablet.

## Introduction

Nitrazepam is used as a hypnotic and sedative drug in the treatment of mental diseases. It is practically insoluble in water (Florey,1980). The bioavailability of nitrazepam after oral administration is highly erratic: 53 to 94% of the drug is absorbed (Reider,1973). The large volume of distribution (2.4 $lkg^{-1}$ of the body weight), longer half-life (8-36 hrs) and narrow therapeutic window (28.2 to 45 $ngml^{-1}$ plasma content) of the drug limits its use as a controlled release dosage form (Lisalo *et al.*1977). Nevertheless, the bioavailability can be improved by increasing the aqueous solubility of the drug using solid dispersion technique. This technique has been utilised to improve the biopharmaceutical properties of many drugs of low aqueous solubility (Ghaly and Abdullah,1986; Summu,1986; Jatovita *et al.*1986; Udupa,1987; Manchanda and Nikore,1988; Rani *et al,*1991; Chowdhary and Ramesh,1994 ). In the present work, solid dispersions (s d) for nitrazepam in PEG and PVP polymers were assayed to improve its dissolution rate. Spectral analyses (Infrared

* Correspondence

spectroscopy and X-ray diffraction) were also carried out to explore the possibility of degradation of the drug by chemical interaction with the polymers and change in the physical state of the drug. With a view to have appropriate dosage form, it was proposed to prepare tablets from these solid dispersions and compare their physical properties with the marketed one.

## Materials and Methods

### *Materials*

Nitrazepam (Cipla, India), polyvinylpyrrolidone (PVP) 14000 and 44000 (CDH, India), polyethylene glycol (PEG) 4000, chloroform, acetone (SD's Fine Chem. Pvt. Ltd., India), polyethylene glycol 6000 (S. D. Lab. Chem. Pvt. Ltd., India), methanol (Spectral grade), hydrochloric acid (AR grade) (Ranbaxy Lab. Ltd., SAS Nagar, India), dicalcium phosphate (DCP Apex Chemicals, India), microcrystalline cellulose (NuChem., India). All other chemicals were of analytical grade.

### *Methods*

*Preparation of physical mixture :* Physical mixtures were prepared by mixing accurately weighed quantities of the drug and polymers polyethylene glycol (PEG 4000 and 6000) and polyvinylpyrrolidone (PVP 14000 and 44000) by triturating in a mortar and sieving the product through sieve no. 40(B.S.S.).

*Preparation of solid dispersion:*

(a) *Solvent fusion (Melt) :*The required quantity of drug was dissolved in methanol, then added to the polymer by stirring and melted into water bath (50°-60°C). This mixture was kept in the water bath until solvent was evaporated. Afterwards, it was cooled to room temperature and passed through sieve no. 40 (B. S. S.).

(b) *Coprecipitation:*The required quantity of polymer and the drug were mixed and then the solvent was added to obtain clear solution. The solution was first dried under vacuum at room temperature and then kept inside incubator (37$^0$C) for 12 hrs. Finally, it was passed through sieve no. 40 (B. S. S.). Three different solvents (acetone, methanol, chloroform) and drug: polymer ratios (1:19, 1:9 and 1:4 that are 5%, 10% and 20% w/w drug, respectively) were taken for the study. The prepared batches are listed in Table 1.

*Drug Content:* Nitrazepam was extracted from the accurately weighed samples into methanol and diluted with 0.1 N HCl. The diluted samples were assayed spectrophotometrically (Beckman Model) at 262 nm using 0.1 N HCl as blank. The concentration was determined from the standard curve prepared in the range 0-14 $\mu gml^{-1}$

*Dissolution Rate of Solid Dispersions:* Dissolution tests were carried out in standard U. S. P. XXIII dissolution rate test apparatus using a paddle stirrer (U. S. P. Apparatus 2) in

distilled water( 900 ml ). The stirring rate was fixed at 100 rpm and the temperature was maintained at 37±1$^0$C. The solid dispersion containing 15 mg of nitrazepam was used for dissolution studies upto 2 hrs. 5 ml samples were withdrawn at 5, 10, 15, 30, 45, 60, 90, 120 minutes time intervals. The same volume was replaced with distilled water. The samples were then diluted with 5 ml of 0.1 N HCl and absorptions were measured spectrophotometrically at 262 nm.

*Solubility Studies:*Solid dispersions equivalent to 10 mg of nitrazepam were taken and placed into glass vials containing 20 ml of distilled water (pH 6.8). The vials were shaken for 6 hrs. and then kept at room temperature. After 24 hrs the solutions were filtered, diluted and assayed for nitrazepam content.

*Spectral Studies of Solid Dispersion:*Infrared spectrophotometry (IR) was performed using KBR pellets (Perkin Elmer 883). X-ray powder diffraction patterns were obtained using an X-ray powder diffractometer (Philips PW 1017). The diffractograms were run at 5$^0$mm$^{-1}$ in terms of 2θ angle.

*Preparation of Tablets:* The batch $L_1$ coprecipitate was mixed with granulated dicalcium phosphate, microcrystalline cellulose and talc for direct compression. Manesty E-2 type single punch tablet machine with a punch of 8 mm diameter was used.

| Tablet formulation | |
|---|---|
| Nitrazepam | 100 mg |
| (in solid dispersion form and equivalent to 5mg of Nitrazepam) | |
| Dicalcium phosphate (granules) | 30 mg |
| Microcrystalline cellulose | 17 mg |
| Talc | 3 mg |

Each tablet weighs 150 mg.

*Dissolution Rate of Tablets*: Method described for dissolution rate studies of solid dispersions was followed except that volume of dissolution media was 300 ml.

*Stability Studies of Nitrazepam Tablets:* The formulated and marketed tablets were placed in amber coloured bottles and kept in ovens previously set at temperatures 45$^0$C, 70$^0$C and 100$^0$C for 30 days. The data obtained at higher temperature can be satisfactorily used for determining the stability at room temperature by extrapolation using Arrhenius model. The drug content of tablet was determined at every 5 days interval to observe the time at which drug concentration reduces below the 90% of the original concentration.

## Results And Discussion

All the dispersions prepared were found to be fine and free flowing powders with uniformity in the drug content. The solid dispersions gave fast and rapid dissolution of nitrazepam(NT) when compared to pure drug and physical mixture (Fig. 1 and 2). The lower release of the drug from physical mixture may be due to the lack of intimate contact between the drug and the polymers. The solid dispersions prepared by solvent fusion

(melting) process resulted in faster and better dissolution (Batch $B_1$; 98% drug release in 0.5 hrs) than the coprecipitation method (Batch $C_1$) (Fig. 1).

The molecular weight of the polymers also affected the release of the drug. PEG 4000 (Batch $C_1$) gave better dissolution of the drug than PEG 6000 (Batch $F_1$) (Fig. 1). It was observed that the heat of solution of solid dispersion system with lower molecular weight polymer is less than that of polymer with higher molecular weight (Najib *et al.* 1987). This may possibly be the reason for increased dissolution rate of the drug with polymer of lower molecular weight .

The solvent used in the preparation of the solid dispersion also plays an important role in the release of the drug. Chloroform provided better dissolution rate of nitrazepam than methanol and acetone in the coprecipitation method (Fig. 1). It could be due to the difference in crystalline nature and hence the energies of the solid dispersions obtained when they were precipitated from the solvent (Najib *et al.* 1986). The crystalline nature of coprecipitate systems may become progressively more stable in the order of chloroform, methanol and acetone.

The drug: polymer ratio (% w/w drug) also affected the release of the drug from the solid dispersions. The drug: polymer ratio of 1:19 (5% w/w drug) resulted in maximum amount of drug release (Fig. 2). At low amounts of the drug, the polymers completely envelope the drug molecule. This increases the wettability and dissolution rate of the drug as the polymers are very soluble.

*Solubility Studies:* The data obtained indicates that the PVP's were more effective in increasing the solubility of the drug in comparison to PEG's (Table 2). Maximum solubility was obtained with PVP 44000 solid dispersion with chloroform (Batch $L_1$).

**Spectral Studies**

*IR Spectra:*The IR studies showed no change in the spectral characteristics of drug both pure and in solid dispersion form (Fig. 3). It suggests that there was no chemical interaction between the polymer and NT.

*X-ray Diffraction:*The distinct, high, intense peaks were observed in the X-ray diffraction of the pure nitrazepam (Fig. 4). These peaks suggest that the drug is crystalline in nature. However, the X-ray diffraction of PVP and the solid dispersion did not show any intense peak that are characteristic of the crystal structure (Fig. 5). It reflects that the drug was essentially in amorphous form in the solid dispersion (Backett and Stenlake,1988; Lackman *et al.* 1987 ). The PVP's and PEG's may be inhibiting the crystallization and changing the nitrazepam into amorphous form during the preparation of solid dispersion. The amorphous form has the highest energy of a pure compound and, therefore, produces faster dissolution rate (Chowdhary and Ramesh,1994).

*Tablet Characteristics:* The tablet characteristics such as weight variation, friability and disintegration time were determined for formulated and marketed tablets (Table 3). The average weight of the formulated tablets(FT) was less than the marketed ones. This reflects that the bulk of the tablet can be reduced with solid dispersions. The FT showed more

hardness, disintegration and less friability than the marketed tablets. This may be attributed to the higher pressure required in direct compression of the tablet, incorporation of water insoluble excipient dibasic calcium phosphate and absence of disintegrating agent. The dissolution pattern of NT was better than the marketed one. Marketed tablets showed only 54% release of the drug whereas FT showed about 83% release in 2 hrs. The dissolution profile of the FT was nearly zero order (Fig. 6). This release pattern can be attributed to the solid dispersion of the drug.

*Stability Studies:* It is evident from drug assay data that there was no substantial decrease in the amount of NT in both formulated and marketed formulations (Table 4). This suggests that the product is stable at elevated temperatures for over a period of 30 days. Further investigations will be required for predicting the shelf-life of the product by accelerated stability tests.

Hence, the increase in the dissolution rate of NT from solid dispersions may be attributed to factors like change in physical state of the drug from crystalline to amorphous form, increase in the aqueous solubility and good wettability and dispersibility of NT in PVP's and PEG's . The increased dissolution and aqueous solubility of the drug by the solid dispersion technique may be expected to increase the bioavailability of NT.

Table 1. Description of Batches

| Batch | Polymer | Drug (% w/w) | Solvent | Preparation |
|---|---|---|---|---|
| $A_1 A_2 A_3$ | PEG 6000 | 5, 10, 20 | - | Melt |
| $B_1 B_2 B_3$ | PEG 4000 | 5, 10, 20 | - | Melt |
| $C_1 C_2 C_3$ | PEG 4000 | 5, 10, 20 | Acetone | Coppt. |
| $D_1 D_2 D_3$ | PEG 4000 | 5, 10, 20 | Methanol | Coppt. |
| $F_1 F_2 F_3$ | PEG 6000 | 5, 10, 20 | Acetone | Coppt. |
| $G_1 G_2 G_3$ | PEG 6000 | 5, 10, 20 | Methanol | Coppt. |
| $I_1 I_2 I_3$ | PVP 14000 | 5, 10, 20 | Methanol | Coppt. |
| $J_1 J_2 J_3$ | PVP 14000 | 5, 10, 20 | Chloroform | Coppt. |
| $K_1 K_2 K_3$ | PVP 44000 | 5, 10, 20 | Methanol | Coppt. |
| $L_1 L_2 L_3$ | PVP 44000 | 5, 10, 20 | Chloroform | Coppt. |
| $M_1 M_2 M_3$ | PEG 6000 | 5, 10, 20 | - | P. M. |
| $M_4 M_5 M_6$ | PEG 4000 | 5, 10, 20 | - | P. M. |
| $M_7 M_8 M_9$ | PVP 14000 | 5, 10, 20 | - | P. M. |
| $M_{10} M_{11} M_{12}$ | PVP 44000 | 5, 10, 20 | - | P. M. |

Coppt. : Coprecipitation; P. M. : Physical Mixture

Table 2. Effect of solid dispersion on the solubility of nitrazepam in distilled water

| Batch | Polymer | Drug (% w/w) | Process | Solvent | Solubility g/ml (x $10^{-5}$) |
|---|---|---|---|---|---|
| N | - | - | - | - | 4.02 |
| $A_3$ | PEG 6000 | 20 | Melt | - | 6.50 |
| $B_3$ | PEG 4000 | 20 | Melt | - | 5.80 |
| $D_3$ | PEG 4000 | 20 | Coppt. | Methanol | 4.85 |
| $F_3$ | PEG 6000 | 20 | Coppt. | Methanol | 5.20 |
| $G_3$ | PEG 6000 | 20 | Coppt. | Methanol | 5.50 |
| $I_3$ | PVP 14000 | 20 | Coppt. | Methanol | 7.50 |
| $L_1$ | PVP 44000 | 5 | Coppt. | Chloroform | 9.80 |

N : Pure Nitrazepam

**Table 3. Physical parameters of tablets**

| Parameters | Nitrazepam Tablets | |
|---|---|---|
| | Formulated | Marketed |
| Drug content | 5.4 mg | 5.2 mg |
| Average weight | 156.31* | 553.30 mg** |
| Disintegration time | 8 min. | 5 min. |
| Hardness | 5-5.5 kg | 4-4.5 kg |
| Friability | 0.84% | 1.004% |

The Indian Pharmacoepial limits of weight variation are

* ± 5%

** ± 7.5%

Table 4. Drug assay data at various temperatures

| Temperature | Days | Percentage of Drug | |
|---|---|---|---|
| | | Marketed | Formulated |
| | 5 | 100.00 | 100.00 |
| | 10 | 100.00 | 100.00 |
| $45^0$C | 15 | 100.00 | 100.00 |
| | 20 | 100.00 | 100.00 |
| | 25 | 100.00 | 100.00 |
| | 30 | 99.98 | 100.00 |
| | 5 | 100.00 | 100.00 |
| | 10 | 100.00 | 100.00 |
| $75^0$C | 15 | 100.00 | 100.00 |
| | 20 | 100.00 | 100.00 |
| | 25 | 99.80 | 100.00 |
| | 30 | 99.00 | 99.45 |
| | 5 | 100.00 | 100.00 |
| | 10 | 100.00 | 100.00 |
| $100^0$C | 15 | 100.00 | 100.00 |
| | 20 | 99.60 | 99.89 |
| | 25 | 99.00 | 99.00 |
| | 30 | 98.40 | 98.5 |

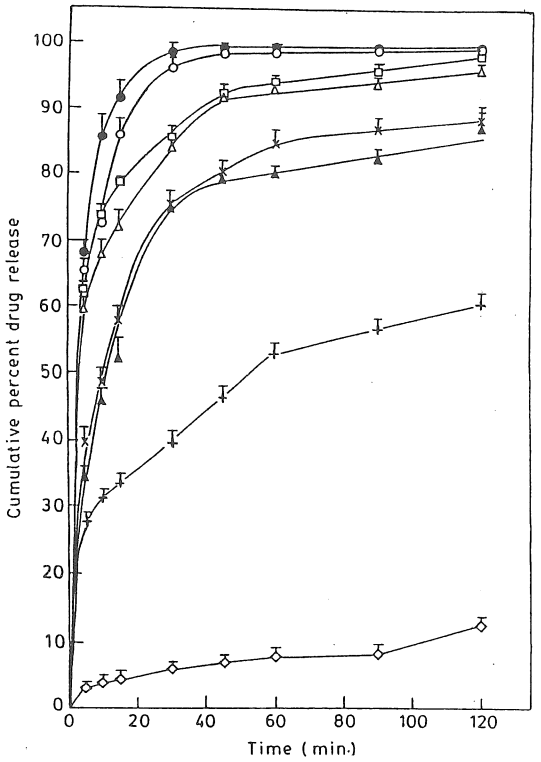


Fig. 1 : Effect of molecular weight of polymer and solvent on the drug release from PEG solid dispersions

Key: • - $B_1$ o - $A_1$ □ - $D_1$ Δ - $C_1$
× - $G_1$ ▲ - $F_1$ + - $M_1$ ◊ - N

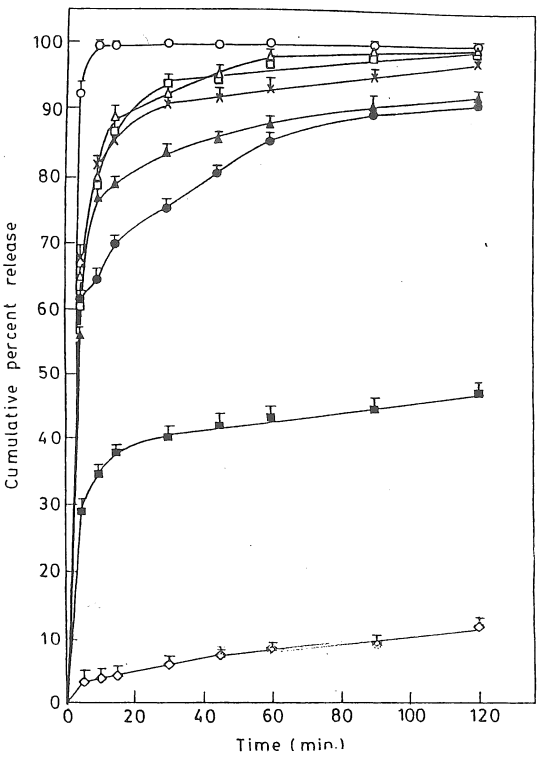


Fig. 2 : Effect of solvent, molecular weight and drug : polymer ratio on the drug release from PVP solid dispersions

Key: O - $L_1$ Δ - $L_2$ • - $L_3$ □ - $K_1$
× - $J_1$ ▣ - $I_1$ - $M_7$ ▲ ◊ - N

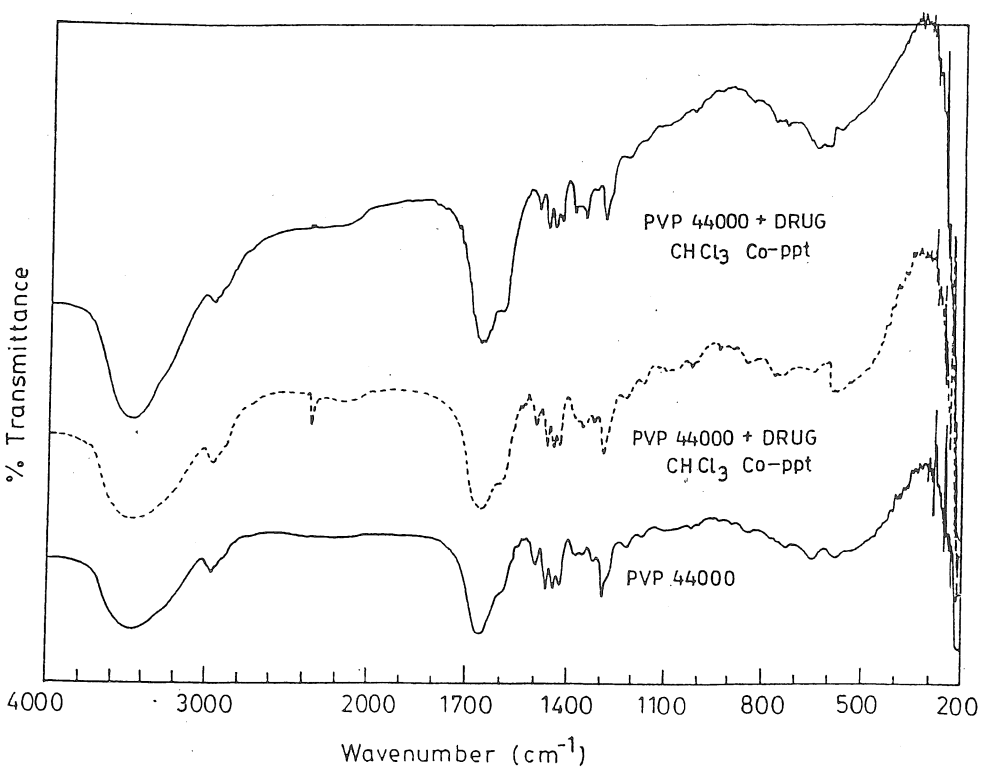


Fig. 3 : Infra-red spectra of PVP-drug solid dispersions and PVP polymer.

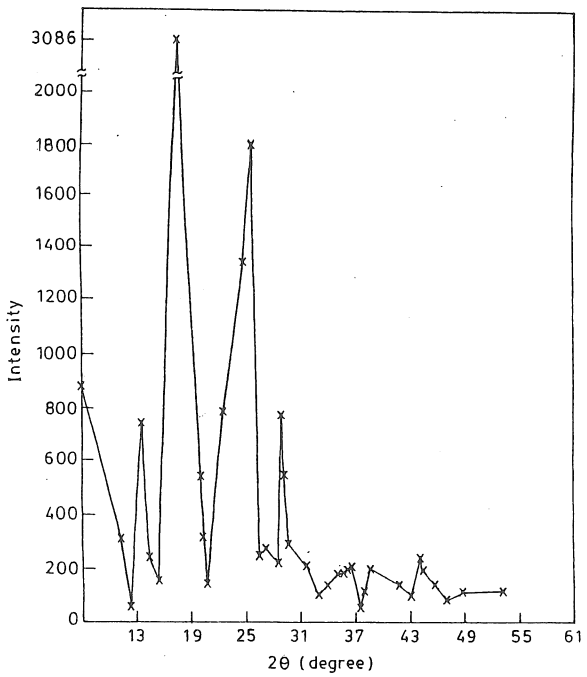


Fig. 4 : X-ray diffraction of pure nitrazepam powder.

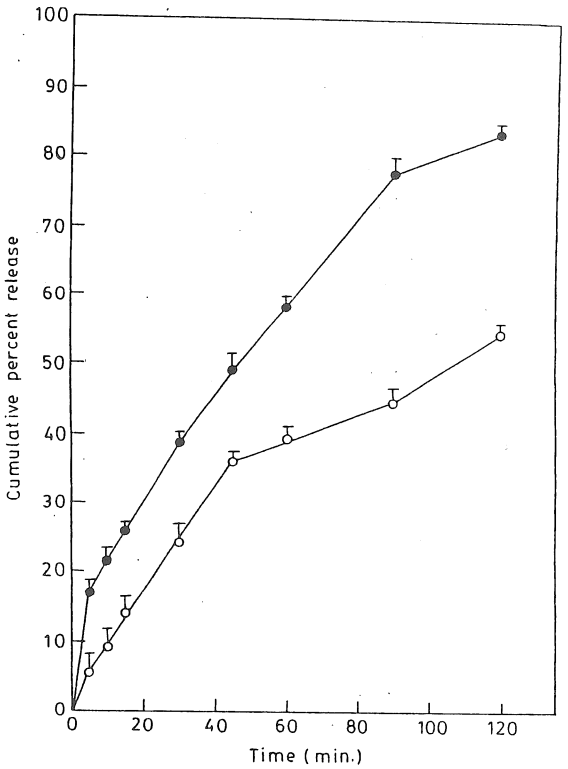


Fig. 6 : Dissolution profile of tablets prepared from solid dispersion and marketed tablets.

Key : • Tablet prepared from solid dispersion.

o Marketed tablet.

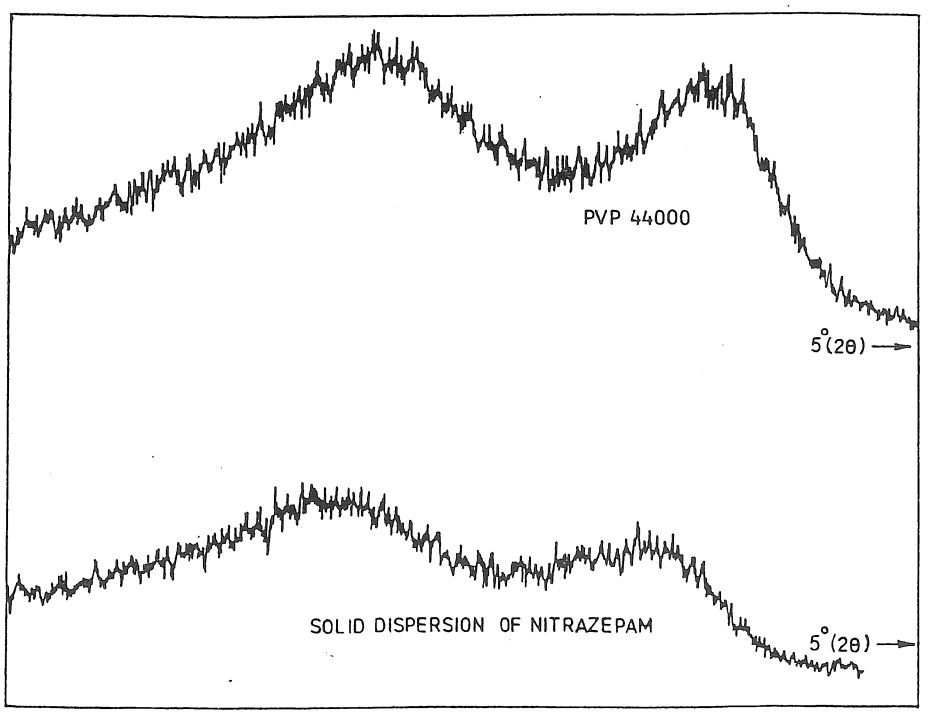


Fig. 5 : X-ray diffraction of solid dispersion of Nitrazepam and PVP-44000.

## REFERENCES


Backett, A. H., Stenlake, J. B.(1988). Practical Pharmaceutical Chemistry, Part II, 4th Edition. Published by The Athlone Press, UK, pp 82-84.

Chowdhary, K. P. R., Ramesh, K. V. R. M. S.(1994). Improvement of dissolution rate and efficiency of nifedipine by solid dispersion in PVP-MCC and HPC-MCC . Ind. J. Pharm. Sci. 56. 95-99.

Florey, K. (1980). Analytical Profiles of Drug Substances 9. 487.

Ghaly, G. M., Abdullah, G.(1986). Dissolution rate study of oxyphenylbutazone crystal form-PEG 6000 binary system. S. T. P. Pharma 2. 209-213.

Jatovita, J. L., Alonso, J., Blanco, J. (1986). Aging of solid dispersion of glyborhuride in PEG 6000. Drug Dev. Ind. Pharm. 12. 1545-1552.

Lackman, L., Herbert, A., Liberman , Kaniga, J. L.(1987). The Theory and Practice of Industrial Pharmacy, 3rd Edition. Published by Vergheese Publishing House, Bombay, pp 180.

Lisalo, E., Kangas, L., Ruikka, I. (1977). Pharmacokinetics of nitrazepam in young volunteers and aged patients(proceedings). Br. J. Clin. Pharmac. 4. 646P-647P.

Manchanda, P. , Nikore, R.L.(1988). In-vitro dissolution and in-vivo absorption enhancement of indomethacin using solid dispersion technique. Indian Drugs. 25.335-337.

Najib, N. M., Mumtaj, A., Sheikh, S.(1987). Release of ibuprofen from PEG solid dispersion-equilibrium solubility approach. Drug Dev. Ind. Pharm. 13. 2263-2275.

Najib, N. M., Suleiman, M., Malakh, A.(1986). Characteristics of in-vitro release of ibuprofen from polyvinylpyrrolidone solid dispersion. Int. J. Pharm. 32. 229-234.

Rani, G. Shoba, Venkatramana, D., Surya Kumar, J. , Krishna, D.R.(1991). Solid dispersions of clofazimine with improved dissolution. Ind. J. Pharm. Sci. 53. 61-64.

Rieder, J. (1973). Plasma level and derived pharmacokinetic characteristics of unchanged nitrazepam in man. Arzneimittel Forsch. 23. 212-213.

Summu, M.(1986). Increasing dissolution rate and GI absortion of nifedipine via solid dispersion. S. T. P. Pharma. 2. 214-220.

Udupa, N.(1987). Effect of crystallinity and solubilizing agent on absorption and excretion pattern of ibuprofen. East Pharm. 30. 137-140.


Accepted: 08.01.2001