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# INCREASING SOLUBILITY AND DISSOLUTION RATE OF NEVIRAPINE BY EMPLOYING SOLID DISPERSION TECHNIQUE USING PLASDONE K 32

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## ABSTRACT

Solid dispersions (SDs) of Nevirapine (NVP) were prepared with the objective of dissolution enhancement by fusion solvent technique using a novel carrier of low molecular weight Plasdone K 32 and at varied concentrations of drug**:** carrier (1:1 and 1:2 ratio). The Fourier transform-IR (FTIR) studies indicated the possibility of hydrogen bonding with the polymer. DSC were used to characterize the solid dispersions, indicated a transformation of drug from crystalline to microcrystalline form. *In vitro* dissolution studies of SDs performed in 0.1 N HCl showed a significant increase in dissolution rates of NVP comparing to physical mixtures and pure drug. Comparatively, SD of NVP: Plasdone prepared by fusion solvent method exhibited higher release rate. Improved dissolution of model drug may be attributed to the modification in drug crystallinity in SDs as was evident from our analytical studies. The dissolution pattern of the NVP from all the SDs followed predominantly first order kinetics compared to Hixson-Crowell's cube root law. This study reflects the vital role of low molecular weight Plasdone as a novel carrier to improve the solubility of NVP, which could minimize the variable dissolution rates with increase in oral bioavailability.

**KEY WORDS:** Nevirapine, Antiretroviral, Solid dispersions, Fusion solvent, Plasdone K 32.

## 1. INTRODUCTION

The most challenging aspects in the pharmaceutical industry are related to strategies that improve the solubility of poorly soluble drugs. The production of solid dispersions (SDs) is commonly acknowledged as a method to enhance the aqueous solubility, thereby increasing the oral bioavailability of drugs with aqueous low solubility (Park,2009). Hence, the formulation of poorly soluble drugs as SDs is a significant area of research aimed at improving their dissolution and bioavailability. The model drug NVP belongs to Biopharmaceutical Classification System (BCS) class II (low solubility/high permeability), poses a challenge in achievement of optimal dissolution kinetics from the dosage form (Jain,2004). NVP is a weak base (pKa= 2.8) with low intrinsic water solubility (0.06 mg/ml) which gives rise to difficulties in the formulation of dosage forms and leads to variable dissolution rates with a resultant decrease in bioavailability (Rang,2006; Usui,1998; Vera,1991). The Plasdone K 32 can be used as a promising model carrier for a wide variety of therapeutic agents due to its excellent physicochemical characteristics such as high aqueous solubility with low toxicity and availability in a wide range of molecular masses (Fernandez,1992). To date, Plasdone K 32s of low molecular weight between 4000 and 130000 have not been reported as a carrier to improve the solubility of poorly soluble drugs. Hence our aim was to explore the possible applicability of Plasdone K 32 (Molecular weight approx. 58,000) as a novel carrier to improve the solubility and dissolution rates of poorly soluble drug NVP through solid dispersion technology.

## 2. MATERIALS AND METHODS

**2.1 Apparatus and chemicals:** Nevirapine (99% purity) was obtained from Hetero drugs Ltd, Hyderabad, India. Plasdone K 32 was procured from R.K. Chem (Pvt.) Ltd., Hyderabad. Other excipients used were of analytical grade. All chemicals used were purchased from Merck, Mumbai, India.

**2.2 Preparation of NVP solid dispersions with PK 32:** The solid dispersions of NVP and PK 32 were prepared by fusion solvent method in a drug: carrier ratio at 1:1 and 1:2% w/w.

**2.3 Physical mixtures:** Previously sieved (mesh 120) NVP and PK32 were accurately weighed and physical mixtures were obtained by blending individual components continuously for 5 -10 minutes with a spatula.

**2.4 Fusion solvent method:** The physical mixtures of NVP and PK 32 were taken in a different beakers dissolved in the soluble solvents like chloroform and methanol according to the ratio and mixed together by their ratio in to the china dish and dried in the incubator at $45^0$C for 3 days.

**2.5.Physicochemical characterization of SDs by FT-IR and DSC:** FT-Infrared spectra of physical mixtures and solid dispersions were obtained using a Perkin Elmer 1600 FTIR spectrophotometer(USA). DSC thermograms of NVP physical mixtures and solid dispersions were performed on a Shimadzu DSC Q20 V24.4.

**2.6 Dissolution testing of Nevirapine marketed tablets in different dissolution media:** Dissolution test was conducted in various dissolution media like distilled water (Nevirapine tablets 200 mg, marketed sample), 0.1 N HCL (active pharmaceutical ingredient, Nevirapine only) 0.1 N HCL (Nevirapine tablets 200 mg, marketed sample) and phosphate buffer Ph 7.2(Nevirapine tablets 200 mg, marketed sample) by using USP 2 Paddle at 50 RPM and the samples were collected up to 120 minutes at equal time intervals to know the release pattern of the Nevirapine from the tablet dosage form as well as dissolution of Nevirapine pure drug in different media.

From the dissolution data we can conclude that (Figures 10-13) Nevirapine drug release was very less in different media mentioned above, particularly during the initial stages of dissolution. So we have decided to improve the dissolution profile of nevirapine by employing novel drug delivery system. We have chosen solid dispersion technique as preliminary screening technique to test whether the drug is suitable for novel drug release system or not. Next we have chosen 0.1 N HCL as dissolution media for testing solid dispersion formulation since 0.1N HCL resembles more of a gastric environment.

**2.7 Dissolution rate determination:** An ELECTROLAB dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 200 mg of the Nevirapine in 0.1N HCL as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2$^0$C, respectively. After fixed time intervals, 10 ml of samples were withdrawn and replaced the same with fresh dissolution media so as to maintain sink condition. The samples were filtered through 0.2µm filters and further diluted with methanol in 25 ml volumetric flasks and these samples were assayed by UV spectroscopy at 263 nm. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

## 3. RESULTS AND DISCUSSION

***In Vitro* Dissolution Study of Solid Dispersion:** The *in-vitro* dissolution of Nevirapine from different drug-polymer ratios was studied. The dissolution rate of Nevirapine from solid dispersion method was significantly higher than Nevirapine alone. This demonstrates the solubilising effects of the Plasdone K 32. The dissolution profiles of solid dispersions prepared using Plasdone K 32 (at 1:2) exhibited significant increase in rate of dissolution in the 0.1 N HCl when compared to the dissolution rate of nevirapine tablets.

## 4. CONCLUSION

In conclusion, solid dispersions increase dissolution rate of Nevirapine. Solid dispersions of Plasdone K 32 had the maximum effect on the rate and extent of dissolution of Nevirapine. The results of this study clearly suggest that fusion-solvent method of solid dispersions is ideal for poorly water soluble drugs.

## 5. ACKNOWLEDGEMENT

The authors are thankful to Hetero drugs Ltd, Hyderabad, India, for providing the gift sample of Nevirapine and Darwin formulations (Pvt.) Ltd., for providing the gift sample of Plasdone K 32, also thankful to Nimra College of Pharmacy, Vijayawada, for providing the necessary facilities to carry out the research work.

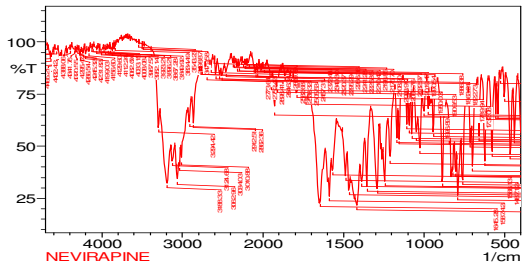


**Fig 1: FTIR spectra of the Nevirapine**

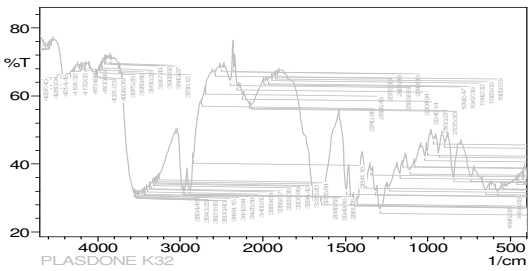


**Fig 2: FTIR spectra of the Plasdone K32**

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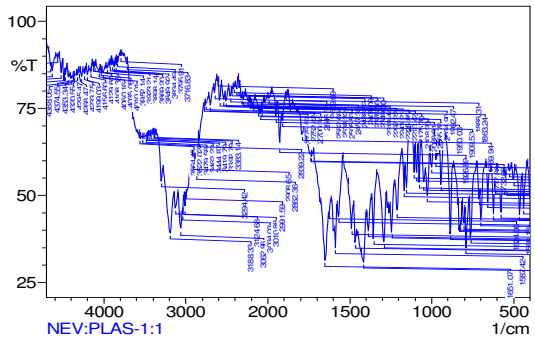


Fig 3: FTIR spectra of the Drug: Polymer (1:1)

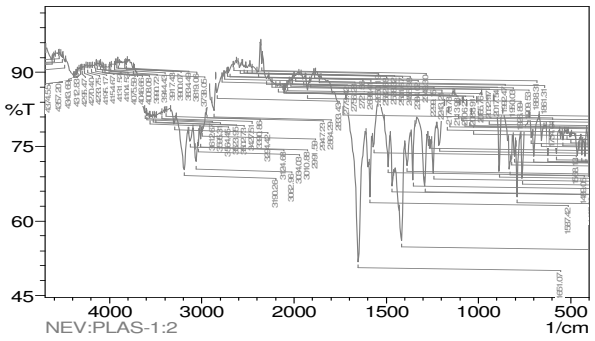


Fig 4: FTIR spectra of the Drug: Polymer (1:2)

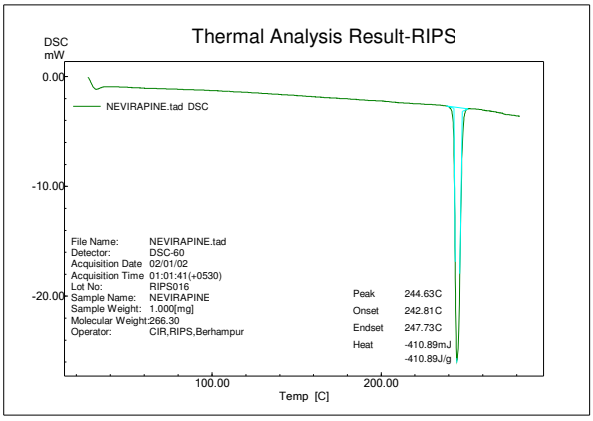


Fig 5: DSC of Nevirapine drug

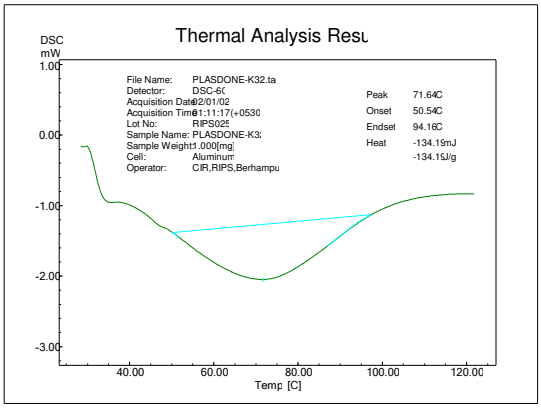


Fig 6: DSC of Plasdone-K32

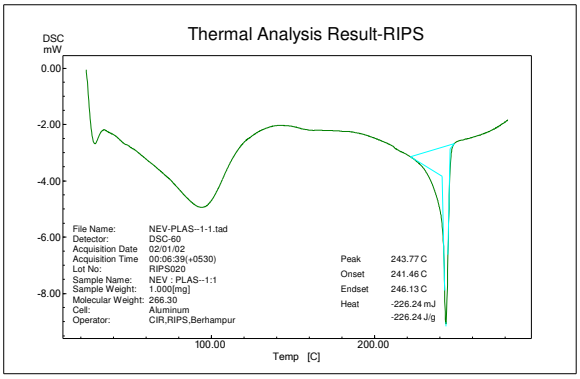


Fig 7: DSC of Nevirapine : Plasdone (1:1)

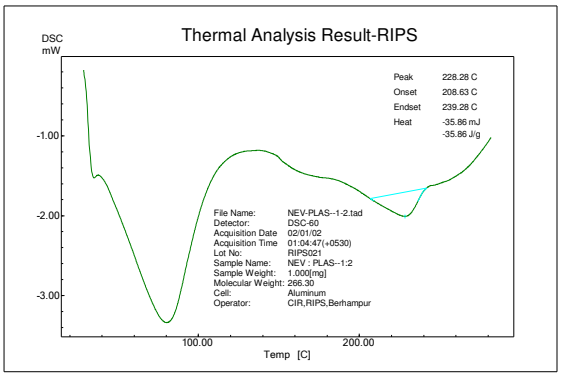


Fig 8: DSC of Nevirapine : Plasdone (1:2)

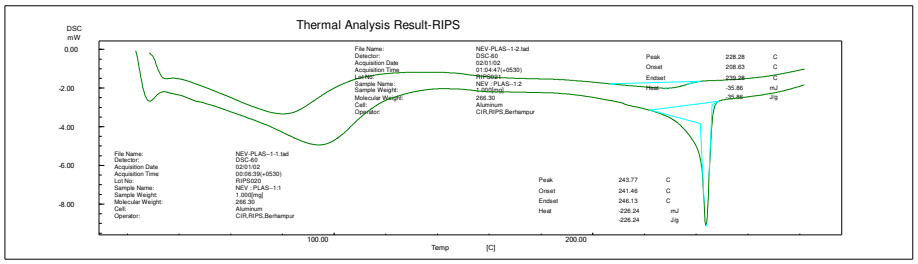


Fig 9: DSC of Nevirapine : Plasdone -1:1vs2

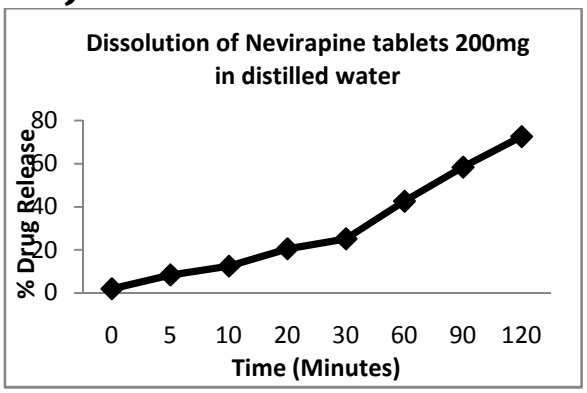


**Fig.10: Dissolution of Nevirapine tablets 200mg in distilled water**

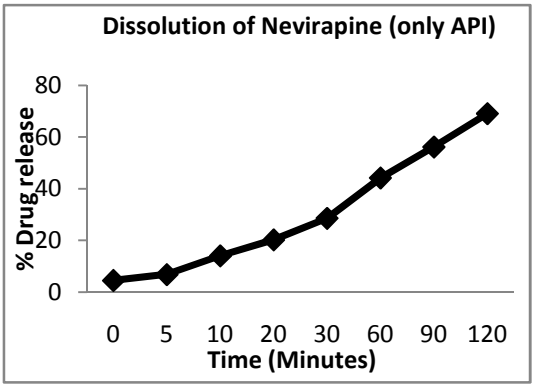


**Fig.11. Dissolution of Nevirapine (only API) in 0.1 N HCl**

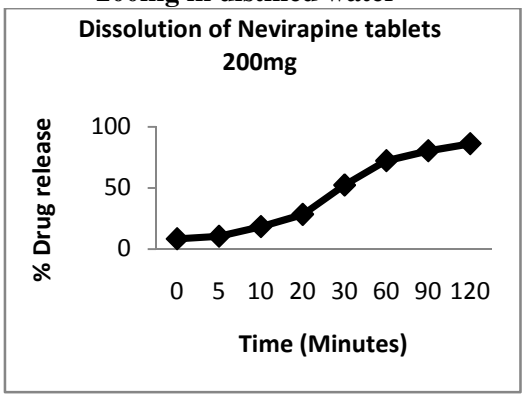


**Fig.12. Dissolution of Nevirapine tablets 200mg in 0.1 N HCl**

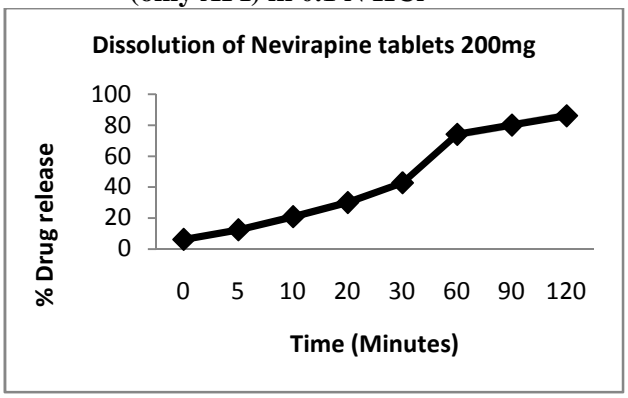


**Fig.13. Dissolution of Nevirapine tablets 200mg in phosphate buffer Ph 7.2**

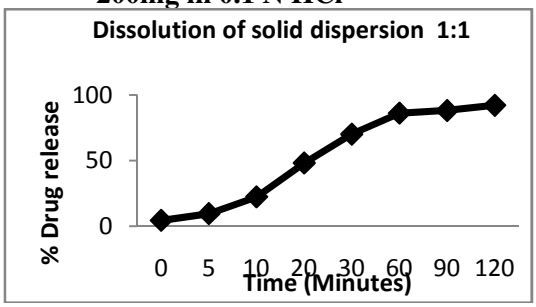


**Fig.14. Dissolution of solid dispersion 1:1 ratio (Drug: Plasdone K 32)**

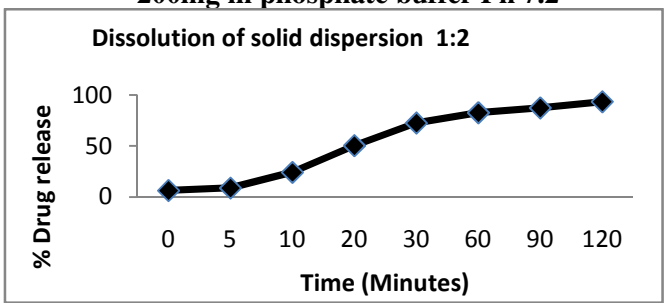


**Fig.15. Dissolution of solid dispersion 1:2 ratio (Drug: Plasdone K 32)**

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