

ENHANCING *INVITRO* BIOAVAILABILITY OF NEVIRAPINE BY EMPLOYING SOLID DISPERSION TECHNIQUE

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ABSTRACT

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (nNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1), HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases alpha, beta, or sigma) are not inhibited by nevirapine. Nevirapine is, in general, only prescribed after the immune system has declined and infections have become evident. The solubility of nevirapine in water is very less 0.7mg/ liter approximately. In order to improve the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate, solid dispersion method is designed and evaluated. Solid dispersions of nevirapine were prepared using PVPK-30 and PEG-4000 separately. Dissolution studies indicated a significant increase in dissolution of nevirapine when dispersed in PVPK-30 and PEG 4000. Solid dispersions containing nevirapine / PVPK-30, 1:2, showed a considerable increase in dissolution in the 0.1 N HCL systems.

KEY WORDS: Nevirapine, PEG 4000, PVPK-30, Solid dispersion, Enhancement in dissolution.

1. INTRODUCTION

To achieve better therapeutic effect of the antiretroviral drugs we need to continue the therapy for longer duration, we need to maintain effective systemic concentration of drug over a long period of time (Park,2009). To maintain consistent drug concentration we need to think of novel approaches in drug delivery systems. Most of the antiretroviral drugs lack systemic bioavailability due to their poor absorption profile (Jain,2004). So in order to reach effective therapeutic concentration we need to administer large doses in frequent intervals of time, this may lead to induce adverse effects and may lack patient compliance (Rang,2006). In order to maintain effective systemic concentration consistently and to avoid unwanted effects due to multiple doses we need to look at novel drug delivery systems. To avoid the unwanted effects due to prolonged usage of the drug in larger doses we have concentrated our study on reducing the dose of the drug by increasing bioavailability. Here we have chosen solid dispersions to achieve the above task.

Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs (Usui,1998). Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique (Vera,1991) has been used by various researchers who have reported encouraging results with different drugs. In conclusion, solid dispersion increases the rate and extent of dissolution of Nevirapine (Fernandez,1992). There are various methods like freeze drying, physical mixing, fusion (melt) method and solvent evaporation are employed for the formulation of solid dispersion and this will helps in the reduction of dose of the drug. Nevirapine was chosen as a water-insoluble model drug and PVPK-30 and PEG4000, as hydrophilic polymers.

2. MATERIALS AND METHODS

Apparatus and chemicals: Nevirapine (99% purity) was obtained from Hetero drugs Ltd, Hyderabad, India. PEG 4000 and PVPK-30 was procured from Darwin formulations (Pvt.) Ltd., Vijayawada. Other excipients used were of analytical grade. All chemicals used were purchased from Merck, Mumbai, India.

Dissolution testing of Nevirapine marketed tablets in different dissolution media: Conducted dissolution testing of Nevirapine tablets 200 mg in various dissolution medias 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 P^H 7.2 (Nevirapine tablets 200 mg, marketed sample) 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 results 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 0.1N HCL as dissolution media for testing solid dispersion formulation since 0.1N HCL resembles more of a gastric environment.

Composition of Solid dispersion: Single component solid dispersions contained 1, 1.5, 2 and 2.5 by weight of PVPK-30 and 1 part of Nevirapine. Another dispersion contained 1, 2, 3 and 4 by weight of PEG 4000 and 1 part of Nevirapine.

Preparation of solid dispersions:

The fusion-solvent method: Accurately weighed amounts of carrier was placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. A solution of drug in methanol was incorporated into the melted carrier with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The pan was then removed from the hot plate and kept in incubator for 24 hours at 37°C. Excipients (1% sodium lauryl sulphate, 5% sodium starch glycolate and 2% magnesium stearate) are accurately weighed and added to it by thoroughly mixing and again kept in the incubator for 24 hours. Finally the powder obtained is pulverized and weighed equivalent to 200mg of drug and dissolution test is carried out.

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 °C, respectively. After fixed time intervals, 10 ml of samples were withdrawn and replace 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 dissolution of Nevirapine from different drug-polymer ratio (Nevirapine /PEG 4000) and (Nevirapine / PVPK-30) is shown in Figures 13 & 14. The dissolution rate of Nevirapine from solid dispersion method was significantly higher than Nevirapine alone. This demonstrates the solubilizing effects of the PEG 4000 and PVPK-30. The dissolution profiles of solid dispersions prepared using PVPK-30 (at 1:2.5) exhibited significant increase in rate of dissolution in the 0.1 N HCl when compared to the dissolution rate of PEG 4000 and nevirapine tablets (marketed sample).

4.CONCLUSION

In conclusion, solid dispersions increase dissolution rate of Nevirapine. Solid dispersions of PVPK-30 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.ACKNOWLEDGEMENTS

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S. No.	Medium	Volume	Apparatus	RPM	Time intervals
1	distilledwater (Nevirapine tablets 200 mg, marketed sample)	900ml	USP2 Paddle	50	0, 5, 10, 20, 30, 60, 90 and 120 minutes.
2	0.1N HCL (active pharmaceutical ingredient, Nevirapine only)	900ml	USP2 Paddle	50	0, 5, 10, 20, 30, 60, 90 and 120 minutes.
3	0.1 N HCL (Nevirapine tablets 200 mg, marketed sample)	900ml	USP2 Paddle	50	0, 5, 10, 20, 30, 60, 90 and 120 minutes.
4	phosphate buffer Ph 7.2(Nevirapine tablets 200 mg, marketed sample)	900ml	USP2 Paddle	50	0, 5, 10, 20, 30, 60, 90 and 120 minutes.

Table1: The dissolution conditions maintained during the studies in different dissolution media are given below

Carrier	Drug: Carrier	Method
PVPK-30	1:1	Fusion-Solvent
	1:1.5	Fusion-Solvent
	1:2	Fusion-Solvent
PEG 4000	1:2.5	Fusion-Solvent
	1:1	Fusion-Solvent
	1:2	Fusion-Solvent
	1:3	Fusion-Solvent
	1:4	Fusion-Solvent

Table2: Composition of Solid dispersion

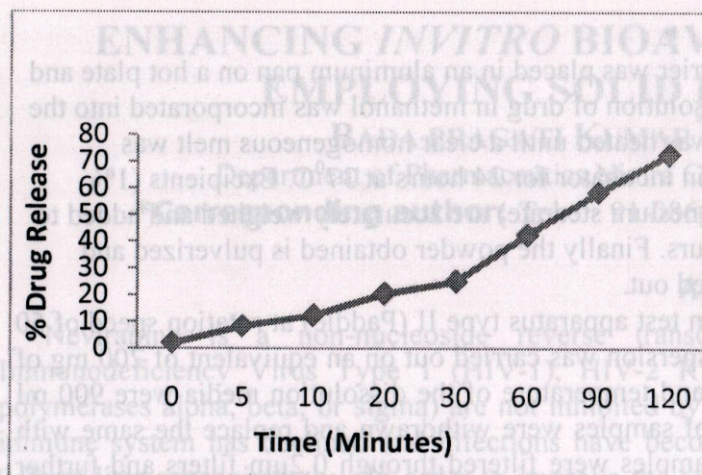


Fig.1. Dissolution of Nevirapine tablets 200mg in distilled water

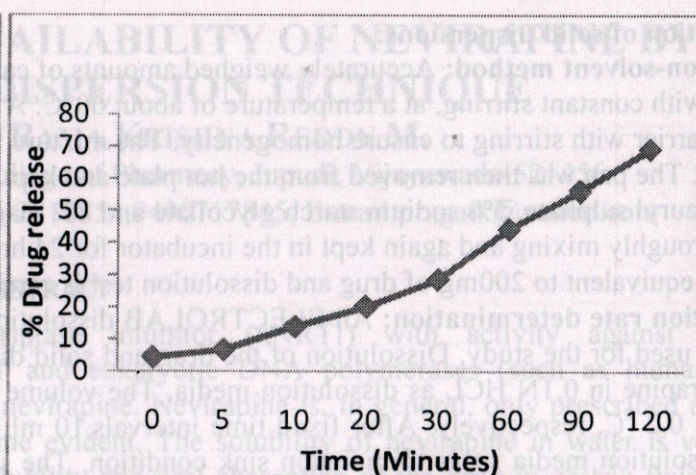


Fig.2. Dissolution of Nevirapine (only API) in 0.1 N HCl

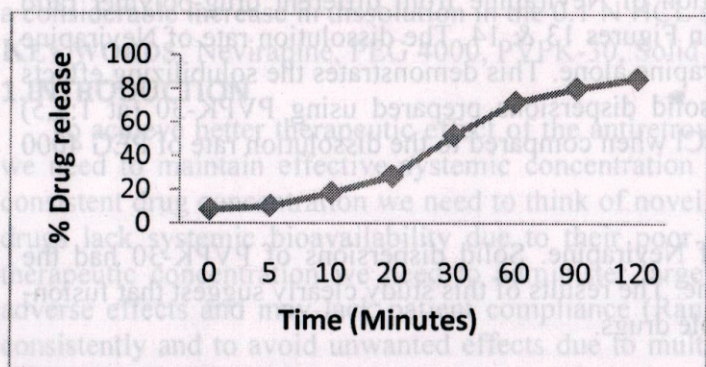


Fig.3. Dissolution of Nevirapine tablets 200mg in 0.1 N HCl

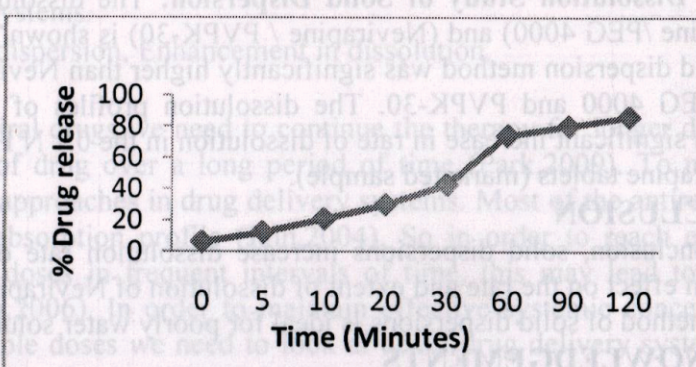


Fig.4. Dissolution of Nevirapine tablets 200mg in phosphate buffer pH 7.2

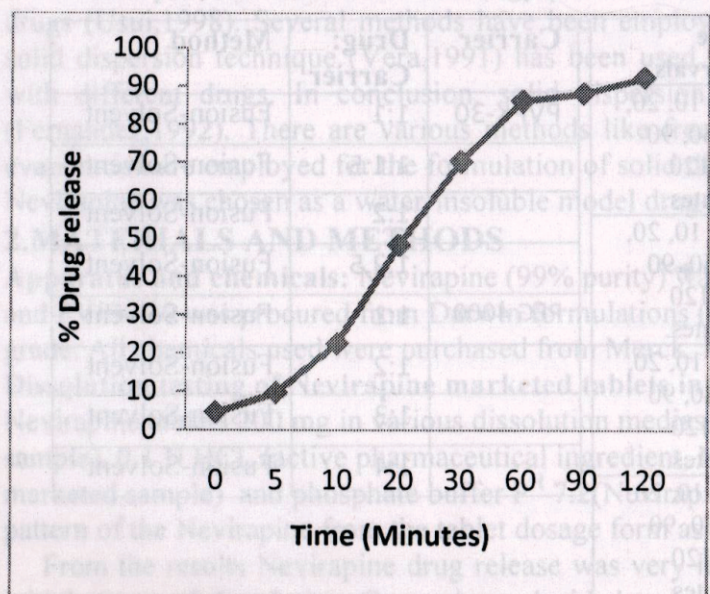


Fig.5. Dissolution of solid dispersion 1:1 ratio (Drug: PVPK-30)

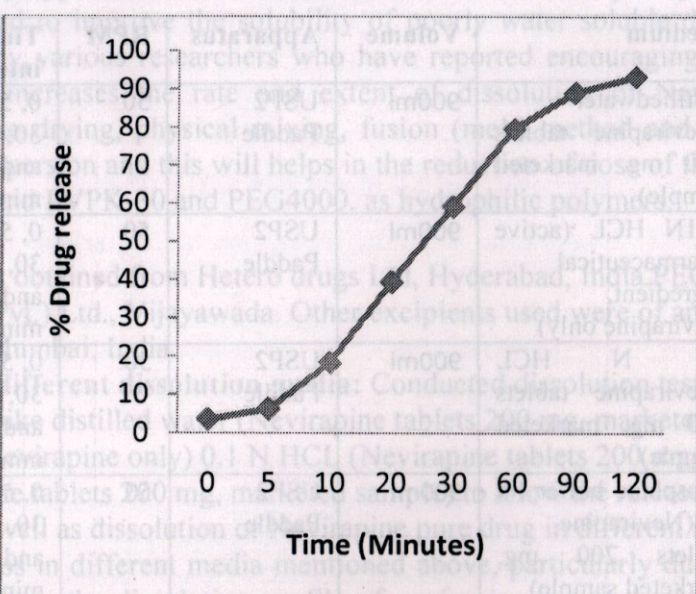


Fig.6. Dissolution of solid dispersion 1:1.5 ratio (Drug: PVPK-30)

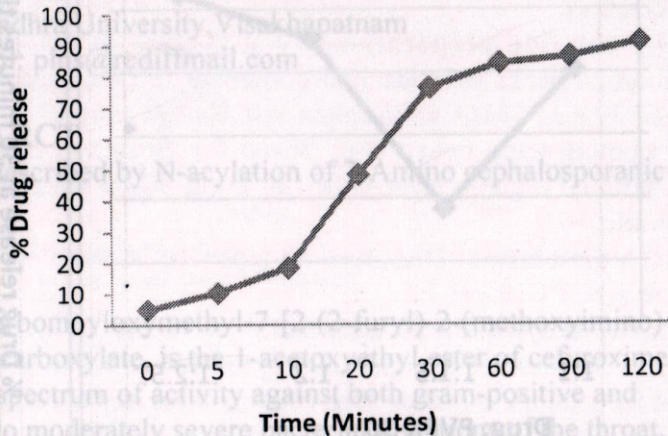
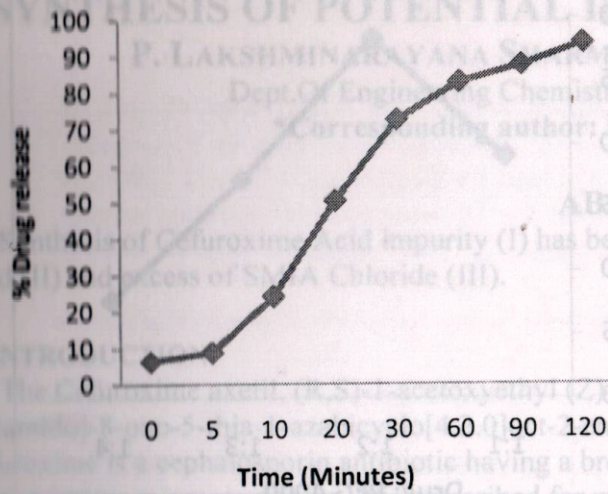


Fig.7. Dissolution of solid dispersion 1:2 ratio (Drug: PVPK-30)

Fig.8. Dissolution of solid dispersion 1:2.5 ratio (Drug: PVPK-30)

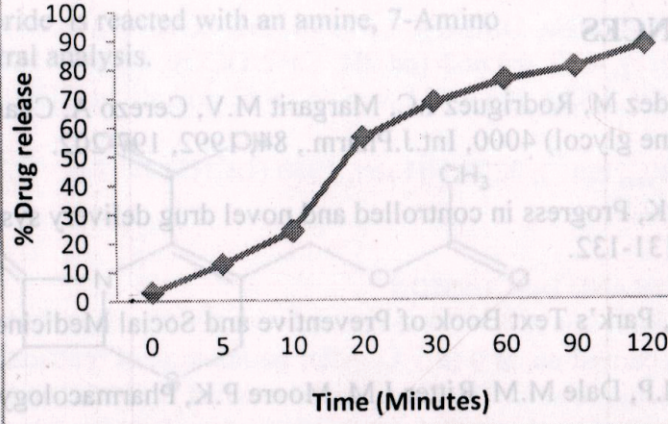
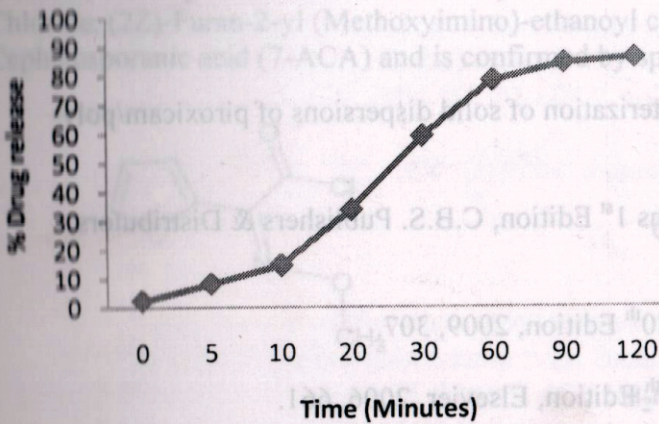


Fig.9. Dissolution of solid dispersion 1:1 ratio (Drug: PEG 4000)

Fig.10. Dissolution of solid dispersion 1:2 ratio (Drug: PEG 4000)

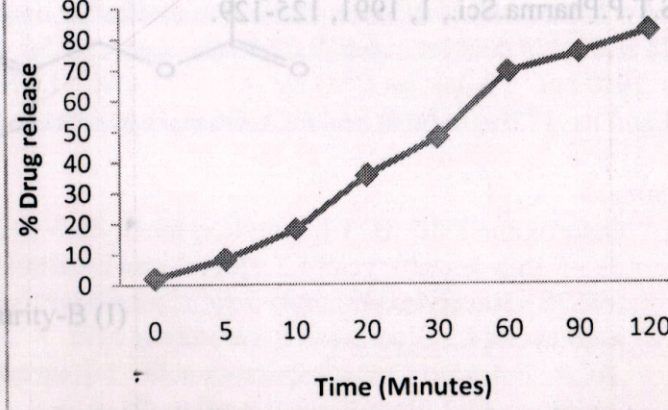
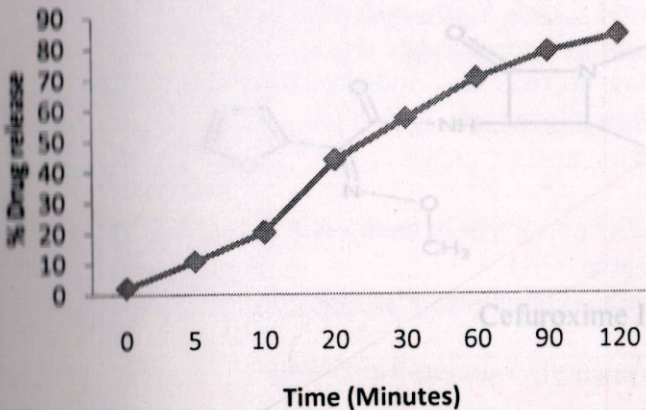


Fig.11. Dissolution of solid dispersion 1:3 ratio (Drug: PEG 4000)

Fig.12. Dissolution of solid dispersion 1:3 ratio (Drug: PEG 4000)

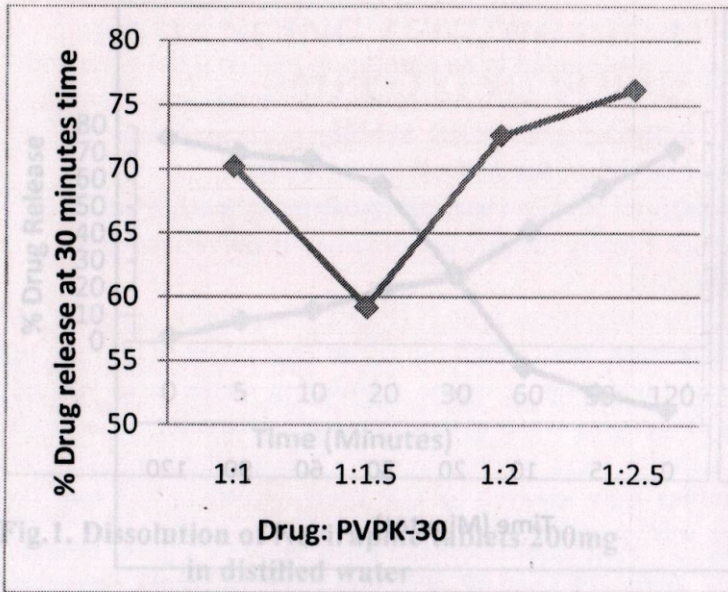


Fig.13. % Drug release at 30 minutes for various ratios of Drug: PVPK-30

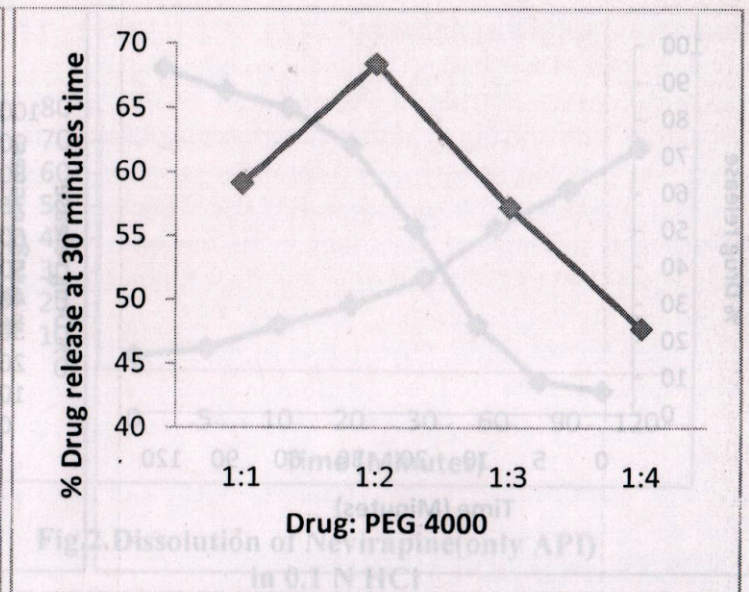


Fig.14. % Drug release at 30 minutes for various ratios of Drug: PEG 4000

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