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Solubility Enhancement of Poorly Water Soluble Drug by Solid Dispersion Techniques

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Abstract: The objective of present was to improve the solubility of Nevirapine by solid dispersion techniques using Polyvinylpyrrolidone K 30 (PVP K 30) as carrier. The Solid dispersion was prepared by physical mixing, solvent evaporation and kneading method. The interaction of the Nevirapine with PVP K 30 was evaluated by the Fourier transform infrared (FTIR) spectroscopy; Differential scanning Calorimetry (DSC), X-ray diffraction patterns (XRD). The results from the FTIR and XRD analyses showed that Solid dispersion might exist in the amorphous form. A DSC result showed that the sharp melting point was completely disappeared suggesting that the Nevirapine molecularly dispersed in an amorphous form. Saturation solubility and dissolution studies indicate that dissolution rate was remarkably increased in Solid dispersion as compared to the physical mixture and drug alone. In conclusion PVP K 30 can be a well utilized to increase the solubility of poorly water soluble drugs.
Key Words: Nevirapine, solid dispersion, Polyvinylpyrrolidone K 30, Saturation solubility.

1 Introduction

Human immunodeficiency virus (HIV) related acquired immune deficiency syndrome (AIDS) has claimed over 25 million lives since its discovery in 1981. Based on the profound knowledge gained about the HIV replication cycle, several drug targets have been identified over the years and effective treatment options are currently available [1]. The current clinical therapy, known as 'highly active antiretroviral treatment' or HAART, is considered as one of the most significant advances in the field of HIV therapy [2].

Nevirapine is the most important drug used in the HAART. Nevirapine is a BCS class II [3]compound with poor aqueous solubility optimum permeability, poses a challenge in achievement of optimal dissolution kinetics from the dosage form. The pH solubility profile indicated a gradual decline in solubility with an increase in pH from 1.5 (1.9mg/ml) to 4 (0.1mg/ml) and remained steady at higher pH (0.1mg/ml at pH 8) [4]. Nevirapine is a small, lipophilic molecule that is rapidly absorbed orally, Nevirapine particularly at higher doses (> 50 mg) exhibit characteristics of solubility rate limited absorption with a resultant decrease in bioavailability [5]. The solubility can be increased using various techniques which include solid dispersion, solvent disposition, cosolvents, salt formation, pH control, Micronization, cogriending [6]. However, all these techniques have potential limitations. All poorly water soluble drugs are not suitable for improving their solubility by salt formation. Decreasing particle size increases solubility but there is poor wetting and flow. Solid dispersions can overcome these problems [7].

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Chiou and Riegelman defined solid dispersions as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the

active ingredients could exist in finely crystalline, solubilized, or amorphous states"[8]. Among the carriers used in the formation of solid dispersions, Polyvinylpyrrolidone K 30 is the most commonly used. It shows the excellent water solubility and significantly in molecular weight 45000. The molecular size of PVP K 30 favours the formation of interstitial solid solutions [9].

The aim of the present study was to prepare a solid dispersion by physical mixing kneading and solvent evaporation methods using PVP K 30 as a carrier. In order to characterize the prepare dispersions, Fourier transform infrared (FTIR) spectroscopy, Differential scanning Calorimetry (DSC), X-ray diffraction patterns (XRD) as well as saturation solubility and dissolution studies were carried out.

2 Experimental

Nevirapine and PVP K 30 was gift sample from the Emcure pharmaceuticals, Pune, Maharashtra, India. All other reagents and solvents were of analytical grade.

2.1 Preparation of solid dispersions and physical mixtures

2.1.2 Physical Mixtures

Physical mixtures were prepared by simple mixing the accurately weighed (1:1, 1:2, 1:3,) Nevirapine and PVP K30 with the help of spatula for 10 min.

2.1.2. Solid dispersions prepared by solvent evaporation method

Solid dispersions were prepared by using different ratios (1:1, 1:2, 1:3) of Nevirapine and PVP K30. The weighed amount of drug and polymer dissolving in a solvent (Ethanol + water) in 1:1 proportions. Then mixed thoroughly and continuously until a major portion of the solvent used was volatilized and a hard to semisolid mass remained. Complete remove of solvent it is dried in oven at 45 ^{o}c until dryness. The dispersions after drying were pulverized using a glass mortar and pestle. The pulverized mass was then sifted through a #60 sieve to obtain a uniform particle size and stored in a desiccator at room temperature until further use.

2.1.2. Solid dispersions prepared by kneading method

Solid dispersions were prepared by weighed quantities of Nevirapine and PVP K30 (1:1, 1:2, 1:3) placed in a mortar and then the mixtures were kneaded with small volume water for 30 min to produce a homogeneous dispersion. Once homogeneous slurry was obtained, samples where dried in oven at 45^{0}C until dryness. The dispersions after drying were pulverized using a glass mortar and pestle. The pulverized mass was then sifted through a #60 sieve to obtain a uniform particle size and stored in a desiccator at room temperature until further use.

2.2 Assay of Drug content

About 15 mg drug equivalent of physical mixture and solid dispersion (theoretical) were weighed accurately and transferred to 50 ml volumetric flask to which 20 ml 0.1N HCL was added and sonicated for 15 min. Final volume was made up with 0.1N HCL. From this stock solution further dilution were prepared. This dilution was used for the assay for drug content by UV spectrophotometer at 313 nm.

2.3 Saturation Solubility Study

The solubility of Nevirapine in distilled water and pH 6.8 (0.5 % sodium lauryl sulfate (SLS)) was determined. An excess amount of NVP was placed in glass bottles containing 20 ml of solvent. The bottles were thoroughly shaken for 24 h and kept aside for 24 hrs at room temperature. At the end of this period the solution were filtered and the filtrate was collected into dry containers. The solutions were suitably diluted and assayed for Nevirapine content.

2.4 Fourier transform Infrared spectroscopy (FTIR)

Fourier transform infrared (FTIR) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm^{-1}.

2.5 Differential Scanning Calorimetry (DSC)

The possibility of any interaction between the drug and the carriers during preparation of Physical mixture and solid dispersion was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture and solid dispersion using DSC. DSC analysis was performed using Mettler, Toledo DSC 822e, on 1 to 4 mg samples. Samples were heated in an open aluminum pan at a rate of 20°C/min conducted over a temperature range of 40 to 300°C under a nitrogen flow of 50 mL/min.

2.6 X-ray powder diffractometry (XRD)

To determine the powder characteristics, X-ray powder diffraction studies of drug and polymer alone as well as physical mixture, and solid dispersion was performed. X-ray powder diffraction patterns were recorded on Brukar AXS, DH Advance, Germany. The scanning rate employed was 6° min^{-1} over 10 to 50° diffraction angle (2θ) range.

2.7 *In- vitro* Dissolution studies

In-vitro release of Nevirapine from the physical mixture and solid dispersion was performed using USP dissolution apparatus II in a dissolution tester

(Electrolab TDT-08L). In this paddle method, sinkers were used in 900 ml of 0.1 N HCL as dissolution medium maintained at 37±0.5°C and stirred at 50 rpm. Exactly 10 ml aliquots were withdrawn from each jar of the dissolution apparatus at time intervals of 10 minutes for the first one hour, and subsequently at 30 minutes up to 2 hrs. Sink condition was maintained by replacing the volume equivalent to the quantity removed with fresh dissolution medium. These solutions were analyzed at 313 nm by UV spectrophotometer. Same procedure is used for the solvent Phosphate buffer pH 6.8 containing 0.5 % sodium lauryl sulfate (SLS) and these solutions were analyzed at 278 nm by UV spectrophotometer.

Table no 1. Drug content of Nevirapine in its physical mixture, solid dispersion

Sr. no.	Formulation	% Drug Content
1	PM 1:1	94.80±0.35
2	PM 1:2	96.16±0.78
3	PM 1:3	96.67±0.98
4	KM 1:1	95.06±0.77
5	KM 1:2	94.62±0.61
6	KM 1:3	95.28±0.55
7	SEM 1:1	92.13±0.64
8	SEM 1:2	94.86±0.86
9	SEM 1:3	94.48±0.78

Table no 2. Saturation Solubility data of Nevirapine and its physical mixture, solid dispersion in distilled water and pH 6.8 buffer solutions

Sr. no.	Formulations	Solubility in Distilled Water (µg/ml)	Solubility in pH 6.8 (µg/ml)
1.	Pure Drug	102.13±0.99	123.33±1.33
2.	PM 1:1	107.73±0.86	131.05±0.66
3.	PM 1:2	109.18±0.68	136.54±0.59
4.	PM 1:3	108.34±0.11	135.10±0.64
5.	KM 1:1	121.45±0.96	151.99±0.99
6.	KM 1:2	174.81±0.48	217.80±1.93
7.	KM 1:3	146.40±0.65	191.18±0.46
8.	SEM 1:1	114.46±0.83	141.18±1.04
9.	SEM 1:2	159.56±0.61	199.90±0.24
10.	SEM 1:3	139.25±1.46	182.99±0.66

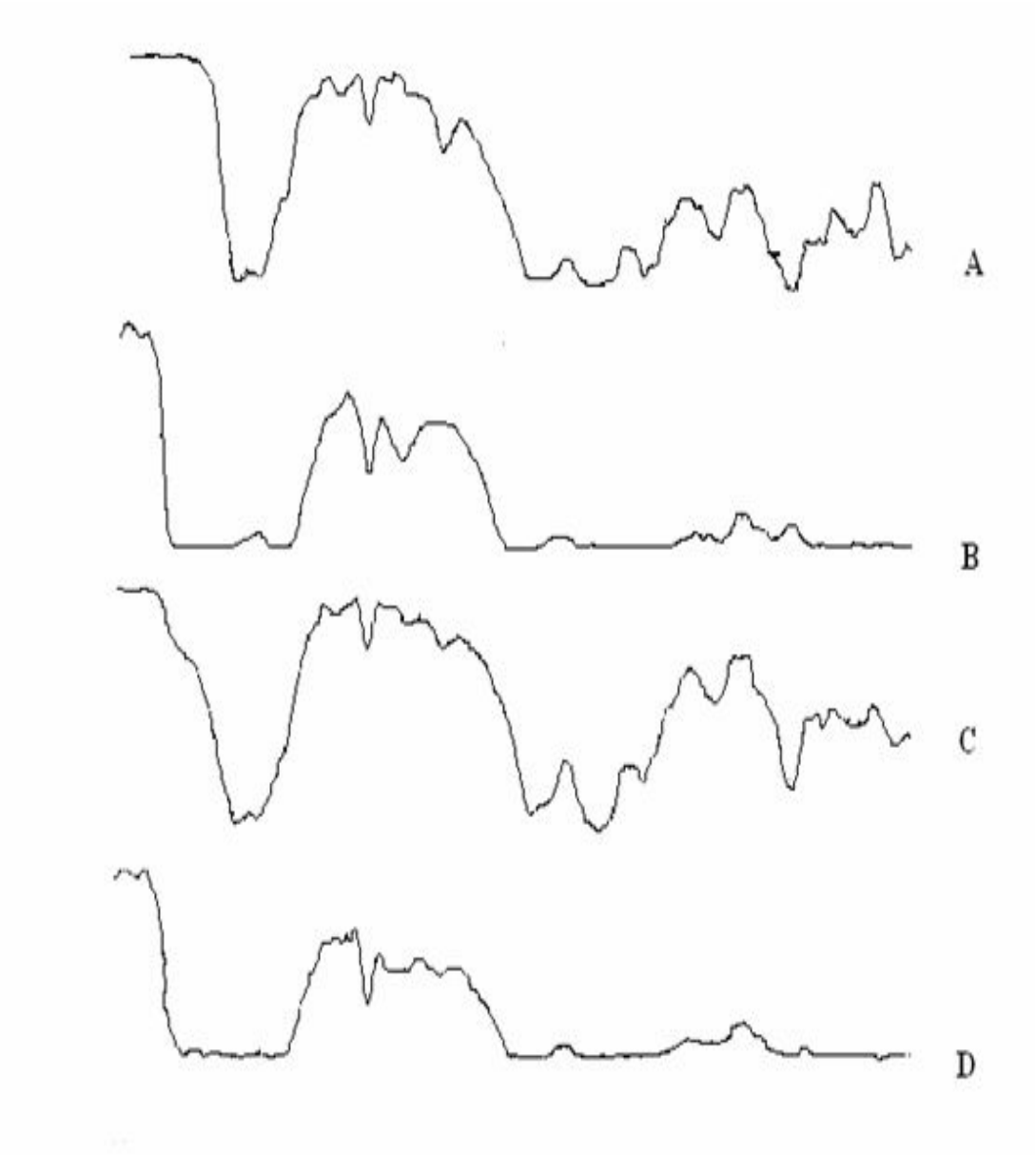


Figure no 1. FTIR Spectrum of (A) Nevirapine, (B) PVP K 30, (C) Physical Mixture, (D) Solid Dispersion (KM 1:2)

Table no 3. Identification of principle peaks in plain drug, physical mixture and solid dispersion (KM 1:2)

IR Band	Drug	PVP K30	
		PM	KM
N-H (S)	3198	3198	3201
C-H (S)	3051.49	3055	3090
C=C	1408-1597	1423	1427,1462
C=O	1643	1643	1643
C-H (B)	690-806	794	775,732

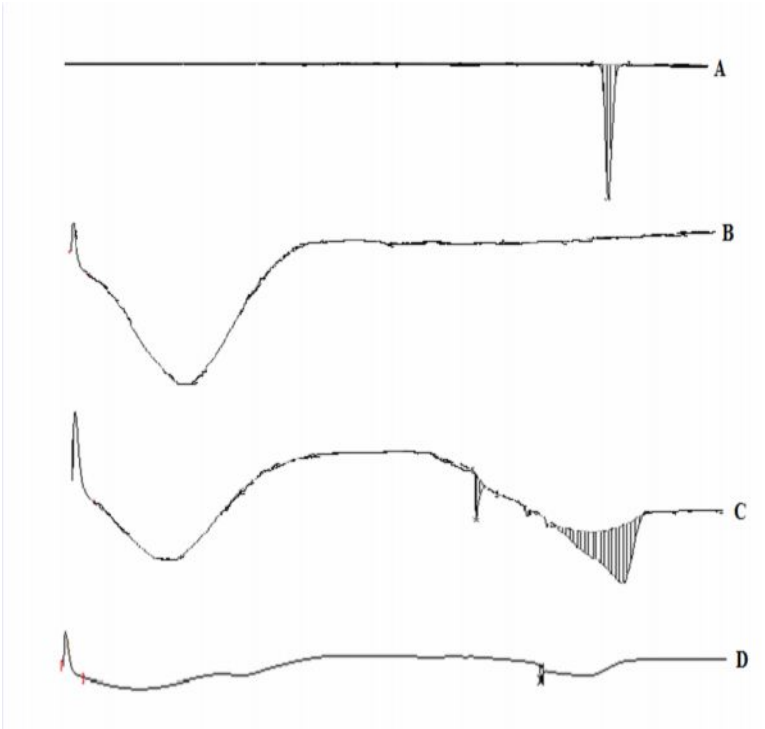


Figure no 2. DSC Thermograms of (A) Nevirapine, (B) PVP K 30, (C) Physical Mixture, (D) Solid Dispersion (KM 1:2)

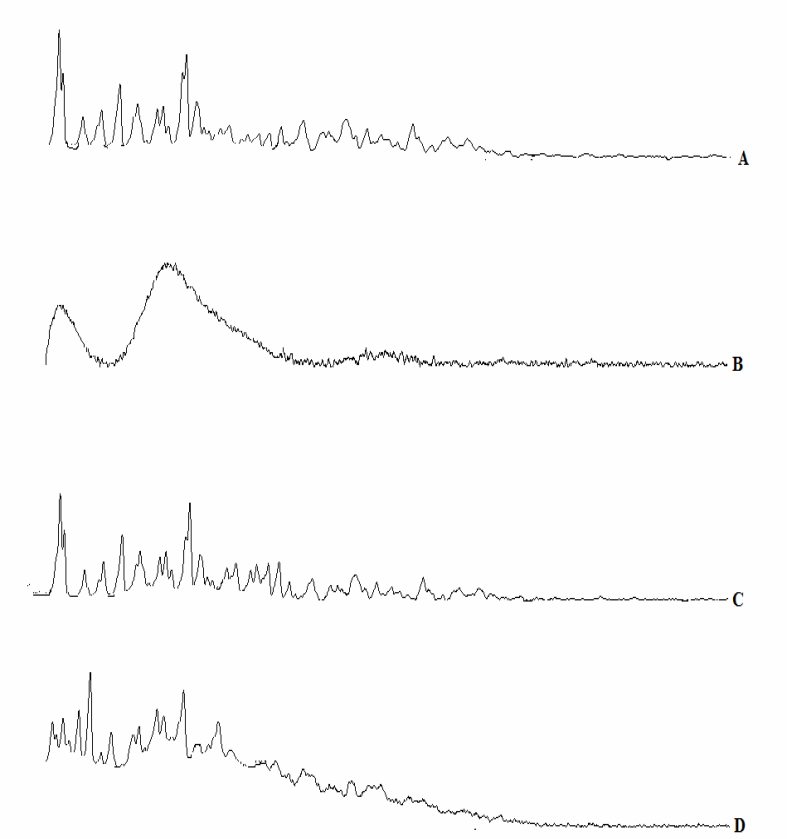


Figure no 3. XRD pattern of (A) Nevirapine, (B) PVP K 30, (C) Physical Mixture, (D) Solid Dispersion (KM 1:2)

Table no 4. Comparative Dissolution profile of Nevirapine and its solid dispersion in 0.1 N HCL by Physical mixture, Solvent evaporation and Kneading Method with PVP K 30

Time	Drug	PM 1:1	PM 1:2	PM 1:3	KM 1:1	KM 1:2	KM 1:3
0	0	0	0	0	0	0	0
10	7.94±0.64	9.11±0.44	9.91±0.54	9.79±0.84	10.08±0.13	11.49±0.22	10.86±0.15
20	9.59±0.09	9.84±0.22	10.98±0.64	10.25±0.74	10.58±0.18	16.29±0.23	15.30±0.22
30	10.61±0.30	11.80±0.15	12.84±0.15	11.74±0.55	13.91±0.13	22.13±0.34	20.09±0.22
40	12.82±0.23	12.99±0.22	15.91±0.22	13.61±0.22	17.26±0.18	27.57±0.30	26.34±0.37
50	13.83±0.32	16.20±0.37	18.70±0.37	16.90±0.47	17.94±0.13	29.81±0.23	29.00±0.16
60	15.00±0.23	19.14±0.22	20.74±0.28	18.14±0.28	20.76±0.14	36.07±0.40	34.31±0.37
90	22.50±0.24	24.45±0.23	26.45±0.28	24.91±0.28	27.44±0.15	48.27±0.45	44.40±0.29
120	27.12±0.24	30.06±0.24	31.55±0.64	30.85±0.64	32.74±0.12	62.49±0.37	48.62±0.37

SEM 1:1	SEM 1:2	SEM 1:3
0	0	0
9.64±0.17	10.13±0.29	9.64±0.17
10.09±0.22	14.32±0.29	12.96±0.23
12.10±0.23	18.55±0.43	17.15±0.23
14.53±0.44	24.68±0.30	23.41±0.26
18.10±0.16	28.10±0.22	26.34±0.23
22.10±0.25	34.49±0.25	32.75±0.23
26.00±0.16	46.72±0.23	43.36±0.38
31.34±0.29	51.60±0.22	46.55±0.50

Figure no 4. Comparative Dissolution profile of Nevirapine and its, solid dispersion in 0.1 N HCL by Physical mixture, Solvent evaporation and Kneading Method with PVP K 30

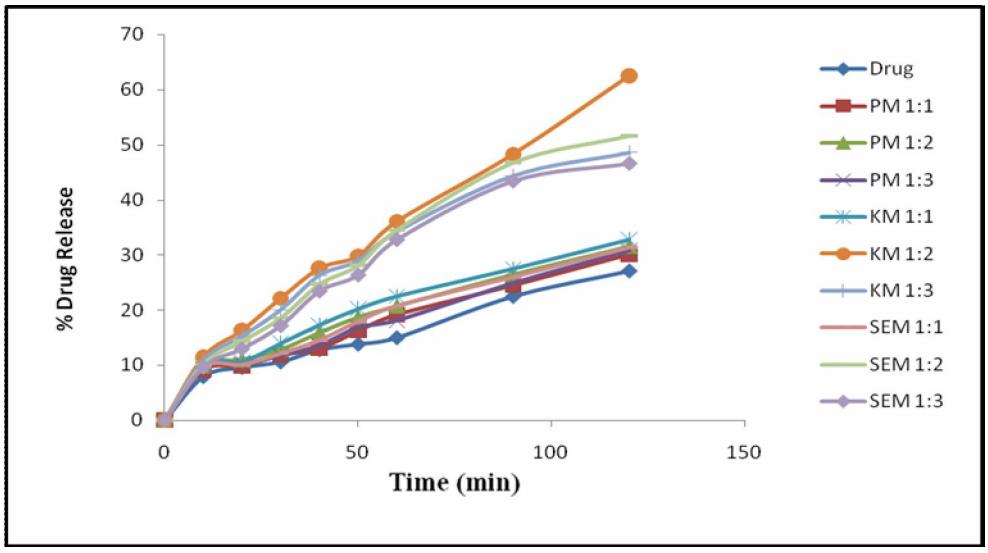
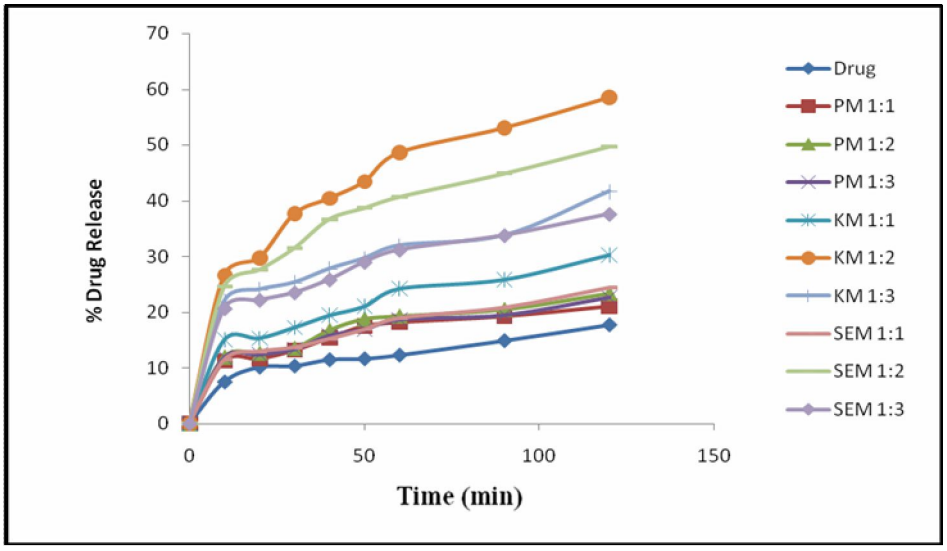


Table no 5. Comparative Dissolution profile of Nevirapine and its solid dispersion in pH 6.8 by Physical mixture, Solvent evaporation and Kneading Method with PVP K 30

Time	Drug	PM 1:1	PM 1:2	PM 1:3	KM 1:1	KM 1:2	KM 1:3
0	0	0	0	0	0	0	0
10	7.51±0.45	11.27±0.91	11.94±0.21	11.87±0.11	15.00±0.61	26.61±0.59	21.96±0.75
20	10.16±0.75	11.69±0.92	12.61±0.22	12.41±0.59	15.32±0.79	29.67±0.61	24.08±0.63
30	10.37±0.74	13.20±0.88	13.50±0.48	13.40±0.84	17.24±0.46	37.62±0.59	25.33±0.61
40	11.50±0.45	15.43±0.80	16.73±0.68	15.83±0.08	19.41±0.90	40.41±0.59	27.79±0.64
50	11.67±0.46	17.57±0.63	18.75±0.56	16.97±0.46	21.01±0.47	43.42±0.75	29.67±0.47
60	12.32±0.79	18.26±0.76	19.26±0.74	18.74±0.15	24.20±0.48	48.63±0.49	31.97±0.45
90	14.92±0.04	19.34±0.77	20.44±0.14	19.54±0.44	25.84±0.46	53.05±0.46	33.79±0.45
120	17.76±0.44	21.13±0.49	23.33±0.87	22.73±0.81	30.27±0.65	58.52±0.44	41.67±0.48

SEM 1:1	SEM 1:2	SEM 1:3
0	0	0
11.47±0.34	24.53±0.59	20.67±0.79
12.98±0.27	27.56±0.62	22.18±0.91
13.71±0.27	31.34±0.60	23.52±0.30
15.25±0.36	36.63±0.97	25.85±0.61
16.90±0.37	38.61±0.31	29.00±0.48
18.96±0.59	40.41±0.59	31.19±0.32
20.85±0.28	44.80±0.80	33.80±0.48
24.43±0.28	49.63±0.47	37.62±0.48

Figure no 5 Comparative Dissolution profile of Nevirapine and its solid dispersion in pH 6.8 by Physical mixture, Solvent evaporation and Kneading Method with PVP K 30



3 Results and Discussion

3.1 Assay of Drug content

. The drug content in all the tested combinations was found to be in the range of 94 to 96% and 92 to 97 % for Physical mixture and solid dispersion respectively. Table no 1 show the percent drug content of physical mixture and solid dispersion.

3.2 Saturation Solubility Study

The results for saturation solubility of NVP and all its physical mixture and solid dispersions are shown in Table no 2. Based on the saturation solubility data, the Formulation Kneading method 1:2 (KM 1:2) showed an exceptional increase in solubility of Nevirapine as compared to other Formulations. It was observed that an increase in solubility of about 1.7 and 1.8 fold with (KM 1:2) as compared to the drug alone in distilled water and pH 6.8. Solubility studies clearly indicated Kneading method of preparing solid dispersions is the method which enhances the solubility greatly as compared to physical mixing and Solvent evaporation because of synergistic effect of trituration and solubilization of used solvent leading to improvement in solubility.

3.3 Fourier transform Infrared spectroscopy

The FTIR spectrum of Nevirapine, PVP K30, physical mixture and, solid dispersions as shown in figure no 1. In the case of PVP K30 and its Physical mixture, Solid dispersion, with Nevirapine, no significant changes were observed between the spectra of the complex and that of the pure drug and PVP K 30 as shown table no 3. Pure Nevirapine spectra showed sharp characteristics peaks at N-H Stretching and C=O at 3198 and 1643 respectively. The spectrum of PVP K30 showed, among others, important bands at 2943.76 (C–H stretch) and 1658.84 (C-O) cm^{-1}. A very broad band was also visible at 3826.90 cm^{-1} which was attributed to the presence of water confirming the broad endotherm detected in the DSC experiments.

3.4 Differential Scanning Calorimetry

Thermal analysis of drug as well as polymer, physical mixture, solid dispersions was carried out using DSC as shown in figure 2. The DSC curve of NVP profiles a sharp endothermic peak at 244.80°C corresponding to its melting, and indicating its crystalline nature. The thermogram of neat PVP K 30 exhibited a broad endotherm ranging from 80 to 120°C was observed due to the presence of water. In the physical mixture of PVP K 30 demonstrated a broadening of the NVP endothermic peak together with a shift to a lower temperature. It could be explained by the formation of crystalline microaggregates of the drug and their considerable dispersions within the amorphous polymeric matrice [10]. A complete disappearance of the drug melting peak was observed in PVP K 30 solid dispersion suggesting that Nevirapine was molecularly dispersed in an amorphous form [11].

3.5 X-ray powder diffractometry (XRD)

X-ray diffractogram of NVP, PVP K30 and their physical mixture, solid dispersion and shown in Figure no 3. The diffraction pattern of the pure NVP showed it's highly crystalline nature, as indicated by the numerous distinctive peaks with major characteristic diffraction peaks appearing at a diffraction angle of 2θ at 13.27°, 25.70° and 41.43°. The spectrum of PVP K30 was characterized by the complete absence of any diffraction peak. The diffraction pattern of PVP K30 Physical mixture and its solid dispersion shows the peaks of NVP with reduction in peak intensities indicating that the conversion of crystalline form to partial amorphous state. These assumptions were found to be in full agreement with the results presented by the DSC and FTIR studies.

3.6 *In- vitro* Dissolution studies

In vitro dissolution data of Nevirapine, physical mixtures and solid dispersions studied in pH 1.2 and pH 6.8 are presented in Table 4 and 5 respectively and dissolution profiles are shown in figure 4 and 5 respectively. The dissolution of drug alone was incomplete even after 120 minutes in both the media studied.

The in vitro release profiles for Nevirapine show that the dissolution of pure drug alone was slow wherein only about 27.12% of Nevirapine had dissolved in pH 1.2 at the end of 2 hrs. The release of drug from formulation of KM 1:2 reached a maximum of about 62.49% at the end of 2 hrs, in pH 1.2 which was the highest amount of drug dissolved the solid dispersions. The in vitro release profiles for Nevirapine show that the dissolution of pure drug alone was slow wherein only about 17.76% of Nevirapine had dissolved in pH 6.8 at the end of 2 hrs. The release of drug from formulation of KM 1:2 reached a maximum of about 58.52% at the end of 2 hrs, in pH 6.8. Following a comparison of the difference in drug dissolution from the pure drug and the solid dispersion in pH 1.2 and pH 6.8, it was observed that KM 1:2 achieved an increase in drug dissolution of about 2.3 and 3.3 fold over the pure drug in pH 1.2 and pH 6.8. Another observation from the Dissolution studies increasing the concentration of the PVP K 30 above 1:2 Drug: polymer ratio it decreases the dissolution rate of the drug due to the higher amount of carrier itself takes more time to dissolve [12]. It was observed that maximum release from the neat drug solid dispersion was obtained in pH 1.2. It was found that the dissolution of Nevirapine followed its solubility pattern i.e. dissolution of the drug was highest in pH 1.2 than the pH 6.8.

References

1. De Clercq E., Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV, Int. J. Antimicrob. Agents, 2009, 33, 307–320.
2. Richman D.D., Margolis D.M., Delaney M., Greene W.C., Hazuda D. and Pomerantz R.J., The challenge of finding a cure for HIV infection, Science, 2009, 323, 1304–1307.
3. Annex 8, Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms WHO Technical Report Series, No. 937, 2006, 413.
4. Sreeraj Machaa *et. Al., In Vitro– In Vivo* Correlation for Nevirapine Extended Release Tablets, Biopharm. Drug Dispos, 2009, 30, 542–550.
5. Panchagnula R., Perumal O. P., and Sarkar Mahua, Solid State Characterization of Nevirapine, Indian Journal of Pharmaceutical Sciences, Sep-Oct 2008, 619-630.
6. Leuner C. and Dressman J., Improving Drug Solubility for Oral Delivery Using Solid Dispersions, Eur. J. Pharm. Biopharm, 2000, 50, 47-60.
7. Patel Manjil, Tekade Avinash, Gattani Surendra, and Surana Sanjay, Solubility Enhancement of Lovastatin by Modified Locust Bean Gum Using Solid Dispersion Techniques, AAPS PharmSciTech, December 2008, 9(4), 1262-1269A.
8. Chiou W. L. and Riegelman S., Pharmaceutical Application of Solid Dispersion Systems, J. Pharm. Sci., 1971, 60 (9), 1281-1302.
9. Van den Mooter G., Augustijn P., Blaton N. and Kinget R., Physico-Chemical Characterization of Solid Dispersions of Temazepam with Polyethylene Glycol 6000 and PVP K30, International Journal of Pharmaceutics, 1998, 164, 67–80.
10. Jr grangeiro S., Strattmann R. R., Alburquerque M. M., Araújo A. A S., Matos J. R. and Rolim P. J., *In vitro* Evaluation of Dissolution Profiles and Thermal Properties of Some Commercial Formulations of Nevirapine Tablets, Acta Farm. Bonaerense, 2006, 25 (1), 76 -82.
11. Kim E., Chun M., Jang J., Lee I., Lee K. and Choi H., Preparation of a solid dispersion of felodipine using a solvent wetting method, Eur. J. Pharm. Biopharm, 2006, 64, 200-205.
12. Kumar N., Jain A. K., Singh C., and Kumar R., development Characterization and solubility study of terbinafine hydrochloride by solvent evaporation method, Asian J Pharm 2008, 154-158.

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