ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Preparation, characterization and *in vitro* evaluation of nevirapine-β cyclodextrin solid complexes

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ABSTRACT

Nevirapine (NVP) is an antiretroviral drug, classified as Biopharmaceutics Classification System (BCS) Class II drug, has a drawback of variable dissolution rates with resultant decrease in oral bioavailability. In the present study, attempts were made to improve the aqueous solubility and dissolution rate of NVP via complexation with β-cyclodextrin (β-CD). The complexation of NVP with β-CD was investigated by phase solubility studies in pH 1.2 and pH 6.8 as the NVP exhibited pH dependent solubility. Solid binary complexes (1:1M) were made by kneading, solvent evaporation and microwave method. All solid complexes were characterized by performing dissolution studies in 0.1 N HCl and pH 6.8 and by analytical techniques such as DSC, FT-IR, P-XRD and SEM. The phase solubility profiles were classified as A_L-type, indicating the formation of 1:1 inclusion complex. Stability constants ($K_{1:1}$) calculated from the phase solubility diagrams were found to be pH dependent. Analytical studies confirmed the formation of inclusion complexes with β-CD. All binary systems exhibited higher dissolution rates in 0.1 N HCl and pH 6.8 than their corresponding physical mixtures and pure drug. The statistical analysis showed that binary system prepared by microwave method was much superior to the others ($P < 0.05$). The release of drug from the preparations is followed predominately first order kinetics compared to Hixson-Crowell's cube root law. The prepared solid complexes reflect the vital role of β-CD to improve the solubility and dissolution rate of NVP, both in gastric and intestinal pH via complexation process, which could minimize the variable dissolution rates with increase in the oral bioavailability.

Keywords: Nevirapine, Antiretroviral, solid complexes, β-cyclodextrin.

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ISSN: 0975-8585

INTRODUCTION

The enhancement of the solubility of poorly soluble drugs is most challenging aspects in the pharma industry. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. According to the biopharmaceutics classification system (BCS), aqueous solubility and permeability are the most important parameters affecting drug bioavailability. Hence, great efforts have been made to improve oral bioavailability of poorly water soluble drugs by increasing their dissolution rate through various techniques [1]. These include the formulation of amorphous solid form, nanoparticles, microemulsions, solid dispersions, melt extrusion, salt formation and formation of water-soluble complexes etc. Among them, the complexations with cyclodextrins are most frequently used.

Cyclodextrins (CDs are a group of structurally related natural products formed during bacterial digestion of cellulose and belongs to a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. They are widely used as "molecular cages" in the pharmaceutical industry, as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability [2,3]. CDs can enhance the aqueous solubility of lipophilic drugs without changing their intrinsic ability to permeate biological membranes through inclusion complexation with various molecules that fit partially or entirely inside the cavity [4]. Cyclodextrin encapsulation of a drug will change the drug's physicochemical properties, such as its aqueous solubility and chemical stability. The cyclodextrin molecule forms a hydrophilic shield around applicable lipophilic moiety of the drug molecule. This will, in general, increase the apparent aqueous solubility of the drug. Reduction of drug crystallinity on complexation or solid dispersion with CDs also contributes to the CD increased apparent drug solubility and dissolution rate. Thus, the contribution of complexation with cyclodextrins will be highly appreciated which modifies the physico-chemical properties such as solubility, dissolution rate and bioavailability of the guest molecules [5,6]. β-cyclodextrin appears to be the best natural cyclodextrin due to its efficient drug complexation, low cost, low toxicity and availability in pure form.

NVP is an orally active antiretroviral drug approved by FDA that is currently used in the treatment of human immunodeficiency virus type 1 (HIV-1) infections [7,8], is particularly insoluble in water at physiological pH conditions and soluble only under extremely acidic media [9].

The model drug 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 [10]. 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 [11,12]. Hence in the present work, inclusion complexes of NVP with β-cyclodextrin were tried, in order to achieve sufficient solubility along the whole gastro-intestinal tract, which is a crucial step in the development of NVP formulations.

MATERIALS AND METHODS

Materials

Nevirapine was kindly supplied by Aurobindo pharma ltd, Hyderabad, India. β-cyclodextrin was purchased from HiMedia Laboratories Pvt Ltd, and Rolex chemical industries, Mumbai, India respectively. All other chemicals and solvents used were of analytical grade.

Methods

Determination of solubility: The solubility of Nevirapine in distilled water, 0.1N HCl (pH 1.2), pH 4.6, pH 6.8 and pH 7.2 was determined. An excess amount of NVP was placed in glass bottles containing 20 ml of solvent. The bottles were thoroughly shaken for 12 h and kept aside for 24 h 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.

Phase solubility studies: Phase solubility studies were carried out in 0.1N HCl and pH 6.8 according to the method described by Higuchi and Connors [13]. Excess amount of NVP (50 mg) was added to 20 ml CD solution (ranging in concentration from 0.015 to 0.03M) prepared in 0.1N HCl and pH 6.8 buffer solution in a series of 100 ml stoppered conical flasks. Then the suspensions were shaken on a rotary at 28^{o}C for 24 h. After equilibrium was achieved, 2 ml aliquots were filtered through 0.45 µm membrane filter and appropriately diluted. The concentration of drug was determined spectrophotometrically at 314 nm. Shaking was continued until three consecutive estimations were the same. The solubility experiments were conducted in triplicate. The blanks were performed in the same concentrations of CDs in 0.1N HCl and pH 6.8 buffer solutions in order to cancel any absorbance that may be exhibited by the CD molecules.

Preparation of NVP: β-CD solid complexes

Solid binary inclusion complexes of NVP:β-CD (1:1 M) were prepared under similar set of conditions by kneading method, solvent evaporation and microwave method. The 1:1 molar ratio was based on the previous solubility studies. All preparations were passed through sieve no.120 and stored in dessicator for further evaluation.

Physical mixtures (PM): The physical mixtures of NVP and β-CD in 1:1 molar ratio were prepared by mixing individual components that had previously been sieved through sieve no.120.

Solvent evaporation method (SE): The aqueous solution of cyclodextrin was dispersed into a solution of NVP dissolved in methanol. The resulting mixture was stirred for 1h and evaporated under vacuum until dry. The dried mass was pulverized and sieved through sieve no.120.

Kneading method (KM): The NVP and β-CD were triturated in glass mortar with small volume of methanol. The thick slurry was kneaded for 1h and then dried at 45^{0}C until dryness. The dried mass was pulverized and sieved through sieve no.120. *Microwave method (MW)*: The aqueous solution of cyclodextrin was added slowly into a solution of NVP dissolved in methanol with constant stirring. These solvents containing glass containers are subjected for irradiation in microwave oven for 90 seconds at 60^{0}c. After reaction was complete, adequate amount of dried methanol added to remove the residual βCD. The resulting mixture was stirred for 1h and evaporated under vacuum until dry.

Analysis of solid complexes in solid state

Fourier Transform Infrared Spectrometry (FT-IR): Solid samples were prepared by the potassium bromide disc method and scanned for absorbance from 400–4000 cm−1. The spectra were obtained on a Perkin Elmer 1600 series, (USA) for NVP, β-CD, physical mixtures and all binary systems.

Differential scanning calorimetry (DSC): DSC Thermograms of NVP, physical mixtures and solid complexes were obtained by using differential scanning calorimeter (Perkin Elmer). Samples (2-5 mg) were sealed in aluminium pans and scanned at a heating rate of 10^{0}C/min over a temperature range of 30 to 300°C under a nitrogen gas stream.

Powder X-ray diffractometry (PXRD): The powder XRD patterns of pure drug, physical mixtures, solid binary and ternary systems were recorded using an X-ray diffractometer (Philips Analytical XRD). Samples were scanned over an angular range of 3-40°; 2θ at a scan rate of 0.01°/sec.

Scanning Electron Microscopy (SEM): The surface morphology of the raw materials and of the binary systems was examined by means of JSM-6400 (Jeol, Japan) scanning electron microscope. The samples were previously fixed on a brass stub using double-sided adhesive tape and were then made electrically conductive by coating with a thin layer of gold and palladium alloy (180-200 Å) using a fine coat ion sputter (JEOL, fine coat ion sputter JFC-1100). The pictures were taken at an excitation voltage of 20 kV and magnification in the range of 118 to 245X.

ISSN: 0975-8585

Analysis of solid complexes in solution state

Drug content uniformity: In each case, complex equivalent to 100 mg of NVP was accurately weighed and transferred to 100 ml volumetric flask and extracted in methanol. The volume was made up to 100 ml with 0.1N HCl. From this, 1ml is subsequently diluted with 0.1N HCl and assayed for Nevirapine content by measuring at 314 nm using 0.1N HCl as blank.

In vitro dissolution studies: *In vitro* dissolution tests were performed for pure drug, physical mixtures and its inclusion complexes using the dissolution test apparatus USPXXIV Type II (Electro Lab, Mumbai, India) by powder dispersion method. NVP (100 mg) or its inclusion complex equivalent to 100 mg of NVP was used in each test. The dissolution studies were carried out using 900 ml of 0.1N HCl (pH 1.2), as well as in pH 6.8 solution maintained at 37 ± 0.5° c with paddle rotation maintained at 50 rpm (n=3). The release of NVP was measured by withdrawing 5 ml samples at regular time intervals, filtered, suitably diluted and assayed spectrophotometrically at 314 nm. Fresh medium was added to maintain a constant volume after each sampling. Dissolution results of pure drug, physical mixtures and solid binary systems were computed by using dissolution software *PCP DISSO V3.*

RESULTS AND DISCUSSION

All solid complexes prepared were found to be fine and free flowing. The drug content was found to be in the range of 97.08 to 102.08 %. Low standard deviation (SD) and coefficient of variation (CV) values in the drug content of NVP:β-CD systems indicated uniform drug distribution in all solid complexes and also ensured the applications of the present methods for the preparation of solid complexes with high content uniformity. The percentage yield of binary systems was in the range of 96.86 % -99.87 % of the initial amounts taken.

Solubility studies: Solubility of drug was determined at 25 ± 0.5°C, in distilled water and wide range of pH solutions of 0.1 N HCl (pH 1.2), pH 4.6, pH 6.8 and 7.2. The solubility results are displayed in Figure 5. Because NVP is weak basic drug (pKa 2.8), an increase in solubility was anticipated with decrease in pH. The pH solubility profile indicated a gradual decline in solubility with an increase in pH from 1.2 (1.703 mg/mL) to 4 .6 (0.252 mg/mL) and remained steady at pH 7 and 7.2 (0.1 mg/mL). The solubility of NVP decreased by approximately, 85% with an increase in pH from 1.2 to 4.6. These results (Table 1) revealed that the solubility of NVP is pH dependent, which is in accordance with the reported literature [14].

Phase solubility studies: The phase solubility diagram for the complex formation between NVP and β-CD studied in 0.1N HCl and pH 6.8 are presented in Figure 1. These plots illustrate that the aqueous solubility of the drug increases linearly as a function of β-CD over the entire concentration range studied and can be classified as A_L-type according to Higuchi & Connors [13]. The linear host (β-CD) –guest (NVP) correlation coefficient with a slope less than 1 indicated the formation of 1:1 water soluble complex with respect to β-CD concentrations. The apparent stability constants ($K_{1:1}$) obtained from the slope of the linear phase solubility diagrams were 339.48 ± 0.73 and 213.98 M^{-1} ± 0.92 in 0.1 N HCl and pH 6.8 respectively. The values indicated that the complexes formed between NVP and β-CD, were quite stable in both media. The calculated $K_{1:1}$ values have depended on the initial solubility of drug (S_0) and the pH of the medium. The values of stability constant ($K_{1:1}$) were found to be higher in 0.1 N HCl than in pH 6.8.

Fourier transform-IR studies: The IR spectrum of NVP exhibit characteristic peaks for amide group (Figure 2) at 3186.40 cm^{-1} and 1647.21 cm^{-1} due to N-H and C=O streching respectively as shown in figure 3A.The IR spectrum of NVP: β-CD complex (1:1M) physical mixture showed peaks at 3194.12 cm^{-1} and 1649.14 cm^{-1} due to N-H and C=O streching of amide group of the drug. Shifts of peaks from 3186.40 cm^{-1} to 3194.12 cm^{-1} of N-H and 1647.21 cm^{-1} to 1649.14 cm^{-1} of C=O indicates a weak interaction between the drug and β-CD (Figure 3C). Similar IR data have been obtained for the NVP:β-CD complex (1:1M) prepared by kneading method confirmed the same weak interaction between the drug and β-CD (Figure 3D)). In the spectra of complexes prepared by solvent evaporation and microwave method, N-H streching of amide group of the drug is shifted towards higher wavelength i.e., 3392.11 cm^{-1} and 3392.69 cm^{-1} respectively (Figure 3E and 3F); suggesting the formation of hydrogen bonds between amide group of the NVP and the hydroxyl group of the host cavities during inclusion complexation. This confirmed the considerable interaction between the drug and β-CD.

DSC Studies: DSC thermogram of pure NVP, β-CD and its binary and ternary solid systems are presented in figure 4. The DSC thermogram of NVP exhibited an endothermic peak corresponding to its melting point (t_{onset} = 245.44 °C, t_{peak} = 249.04 ?C, ΔH = 241.0185 J/g). β-CD showed the broad endothermic peak due to loss of water. In the thermogram of NVP:β-CD prepared by kneading and solvent evaporation method (C and D respectively), the intensity of the endothermic peak at 249°C is reduced, which indicates an interaction between NVP and β-CD. In case of NVP:β-CD complex prepared by microwave method the intensity of the endothermic peak is much reduced that confirmed the formation of complexation of drug with β-CD.

Powder X-ray diffractometry: Comparison between XRD spectra of NVP**,** β-CD, physical mixtures and binary systems are shown in figure 5. The XRD pattern of pure NVP showed more number of peaks that were intense and sharp, indicating its crystalline nature. The spectrum of PVP was characterized by the complete absence of any diffraction peak. The XRD pattern of solid complexes differs significantly from that of the physical mixtures. No inclusion complex was obtained by physical mixtures and the diffraction pattern of all binary systems of NVP:β-CD showed other peaks of NVP with decrease in the intensity of peak indicating the reduction in crystallinity. However in the NVP:β-CD binary systems prepared by microwave method, the crystallinity of NVP was found to be reduced to a greater extent, evidenced by marked reduction in the number as well as the intensity of peaks.

SEM Analysis: Morphological features of the NVP solid complexes were examined by scanning electron microscopy. Figures 6 shows the scanning electron microscopic pictures of (A) NVP, (B) β-CD, (C) NVP:β-CD (KM), (D) NVP:β-CD (SM), (E) NVP:β-CD (MW). NVP existed as irregular shaped aggregates and β-CD appeared as large crystalline particles, whereas the PVP were seen as amorphous or pieces of spherical particles. SEM photographs of binary systems clearly depicted the reduction in NVP drug particle sizes and adhered onto the surface of β-CD. In all systems, the original morphology of two components disappeared and existed as small aggregates of irregular amorphous pieces. Therefore, the reduced drug particle size, increased surface area might be responsible for the increased solubility and dissolution rate of the prepared solid complexes.

Dissolution behavior of solid complexes: Since NVP exhibited pH dependent solubility, dissolution studies of all solid complexes were carried out in both simulated gastric fluid (0.1 HCl ie pH 1.2) and simulated intestinal fluid (pH 6.8). It is also reported that, the absorption of NVP is excellent from the small intestine [15]. Hence the increase in solubility at intestinal pH is also an important strategy to improve the absorption of the model drug.

All solid binary and their corresponding physical mixtures were tested for dissolution properties and compared with the pure NVP. Dissolution data were evaluated on the basis of cumulative percentage drug release, dissolution efficiency and correlation coefficient (r).The percentage of NVP dissolved at 30 min (DP_{30}) and dissolution efficiency at 30 min (DE_{30}) and 60 min (DE_{60}); and the characteristic time for 50% dissolution of NVP (T_{50} min) were calculated for all solid complexes. The dissolution efficiency of all preparations was calculated by the method mentioned by Khan [16].

In vitro dissolution data of NVP, physical mixtures and solid binary complexes studied in 0.1N HCl and pH 6.8 are presented in table 3 and 4 respectively. Best fit models and various dissolution parameters such as RDR_{30}, $DP_{30,}$ DE_{30} and T_{50} for NVP, solid binary systems studied in 0.1N HCl and pH 6.8 are summarized in table 4. The dissolution profiles of NVP alone, physical mixtures and solid binary complexes studied in 0.1N HCl and pH 6.8 are shown in figure 7 and 8 respectively. The dissolution of drug alone was incomplete even after 120 minutes in both the media studied. All binary complexes exhibited higher rates of dissolution and dissolution efficiency values than the physical mixtures and pure drug. To clarify the statistical significance of difference between binary systems and pure drug, one-way ANOVA was used. The statistical analysis showed that binary system prepared by microwave method was significantly superior to the others ($P < 0.05$). The value of T_{50} of all solid binary complexes was much lower than NVP alone. The mean percent drug release from the solid complexes at 30 minutes in 0.1 N HCl was 1.12 (B1), 4.95 (B2), 5.01 (B3) and 5.07 (B4) fold higher when compared to pure drug (Table 4A). According to the obtained results, the rank order of dissolution efficiency (DE_{30}) and percent drug dissolved at 30 minutes (DP_{30}) in pH 1.2 of binary complexes was method dependent and were found in the following rank order,

B4 (MW) > B3 (SE) > B2 (KM) > (B1) PM > Pure drug

Comparatively, dissolution efficiency at DE_{10}, DE_{30} and DE_{60} of solid complex prepared by microwave method was found to be higher when compared with other methods. Improved dissolution rate and dissolution efficiency observed in this case might be due to the formation of solid inclusion complexes, with better interaction of drug and CD during the process.

Similarly mean percent drug release from the solid complexes at 30 minutes (DP_{30}) in pH 6.8 was 1.17 (B1), 3.26 (B2), 4.34 (B3), and 3.82 (B4) fold higher when compared to pure drug (Table 4B). The rank order of the dissolution rates of several systems in pH 6.8 were found in the following pattern,

B3 (SE) > B4 (MW) > B2 (KM) > PM > Pure drug

It was found that the percentage of drug dissolved at 30 minutes (DP_{30}) was higher from solid complexes prepared by solvent evaporation method (B3) compared to that prepared by microwave method (B4). However, the dissolution efficiency (DE_{30}) of B4 was found to be little higher than the B3. This indicates that the pH of the dissolution medium had little effect on the dissolution properties.

As expected, all preparations showed little higher percentage of dissolved drug in pH 1.2 than in pH 6.8, probably due to the favourable solubility of the drug in the gastric juice. However, all the binary systems displayed better dissolution rates in pH 6.8 also with respect to the drug alone. Overall, the *in vitro* results have shown an enhanced dissolution rate of NVP in both gastric and intestinal media from prepared drug-β-CD complexes.

Dissolution profiles of all solid complexes were analysed according to Hixson-Crowell's cube root law and first order kinetics. The correlation coefficient (r) values of the first order kinetics were found to be slightly higher to the 'r' values of Hixson-Crowell's cube root model (Table 4). Hence the release of the drug from the preparations followed predominantly first order kinetics compared to Hixson-Crowell's cube root law.

Table 1: Solubility data of pure NVP in different pH solutions

Solubility	Concentration (mg/1ml) ± SD
0.1N HCl (pH 1.2)	1.703 ± 0.004
pH 4.6	0.252 ± 0.001
pH 6.8	0.114 ± 0.003
Distilled water	0.1 ± 0.004
pH 7.2	0.1 ± 0.006

Table 2: *In vitro* **dissolution data of NVP and solid binary systems in 0.1 N HCl**

Time in minutes	Cumulative percent of drug released (± SD, n=3)				
	NVP	NVP:β-CD (PM)	NVP:β-CD (KM)	NVP:β-CD (SM)	NVP:β-CD (MW)
10	05.32 ± 0.02	00.76 ± 0.21	11.87 ± 0.19	11.87 ± 0.33	12.44 ± 0.35
20	07.59 ± 0.03	04.46 ± 0.17	24.94 ± 0.22	24.94 ± 0.45	26.08 ± 0.54
30	09.85 ± 0.02	07.30 ± 0.18	48.78 ± 0.21	49.35 ± 0.32	49.91 ± 0.71
45	14.67 ± 0.06	16.94 ± 0.27	60.08 ± 0.28	61.78 ± 0.48	62.91 ± 0.38
60	21.46 ± 0.01	23.16 ± 0.26	69.08 ± 0.30	71.92 ± 0.27	74.18 ± 0.28
90	27.94 ± 0.01	29.64 ± 0.11	72.40 ± 0.27	77.50 ± 0.54	80.90 ± 0.45
120	33.29 ± 0.02	37.53 ± 0.25	85.90 ± 0.26	90.99 ± 0.65	94.95 ± 0.38

ISSN: 0975-8585

Table 3: *In vitro* **dissolution data of NVP and solid binary systems in pH 6.8**

Time in minutes	Cumulative percent of drug released (± SD, n=3)				
	NVP	NVP: β-CD (PM)	NVP: β-CD (KM)	NVP: β-CD (SM)	NVP: β-CD (MW)
10	03.33 ± 0.45	03.61 ± 0.56	06.17 ± 0.39	06.74 ± 0.56	07.60 ± 0.34
20	04.75 ± 0.63	05.88 ± 0.70	14.13 ± 0.36	15.27 ± 0.54	18.40 ± 0.39
30	08.15 ± 0.32	09.57 ± 0.57	26.62 ± 0.46	35.42 ± 0.30	31.16 ± 0.29
45	12.40 ± 0.37	13.25 ± 0.38	43.90 ± 0.39	52.70 ± 0.43	48.72 ± 0.47
60	15.79 ± 0.28	16.64 ± 0.39	52.64 ± 0.38	66.81 ± 0.28	63.13 ± 0.59
90	21.15 ± 0.71	23.41 ± 0.63	69.85 ± 0.48	78.91 ± 0.52	76.65 ± 0.39
120	27.06 ± 0.64	29.89 ± 0.48	77.98 ± 0.28	84.77 ± 0.72	90.71 ± 0.30

Table 4: Various dissolution parameters and best model fitting curve values of NVP and solid complexes in (A) 0.1 N HCl and (B) pH 6.8

Batches	DE_{30} (%)	DE_{60} (%)	DP_{30}	T_{50} (min)	RDR_{30}	MDT_{30}	First order rates $K_1 \times 10^2$ (min^{-1})		Hix.Crow $K_{HC} \times 10^2$ ($mg^{1/3}.min^{-1}$)	
							R	K_1	R	K_{HC}
(A) 0.1 N HCl										
NVP	5.95	10.56	9.9	195.0	1	11.90	0.9937	-0.0036	0.9912	-0.0011
NVP:β-CD (PM)	2.96	9.52	7.3	177.1	1.12	17.83	0.9889	-0.0039	0.9889	-0.0039
NVP:β-CD (KM)	20.40	39.96	48.8	41.8	4.95	17.45	0.9776	-0.0166	0.9551	-0.0044
NVP:β-CD (SM)	20.50	40.85	49.4	35.9	5.01	17.54	0.9875	-0.0193	0.9753	-0.0048
NVP:β-CD (MW)	21.16	41.82	49.9	30.9	5.07	17.28	0.9816	-0.0224	0.9856	-0.0053
(B) pH 6.8										
NVP	4.05	8.12	8.2	257.7	1	15.09	0.9976	-0.0027	0.9962	-0.0009
NVP:β-CD (PM)	4.76	8.97	9.6	231.1	1.17	15.07	0.9988	-0.0030	0.9975	-0.0010
NVP:β-CD (KM)	11.21	11.21	26.6	54.8	3.26	17.37	0.9946	-0.0126	0.9938	-0.0035
NVP:β-CD (SM)	13.25	32.5	35.4	42.4	4.34	18.78	0.9905	-0.0164	0.9829	-0.0043
NVP:β-CD (MW)	13.86	30.90	31.2	39.2	3.82	16.66	0.9826	-0.0177	0.9964	-0.0044

Where, DE= Dissolution efficiency after 30 and 60 min, DP= percent of drug dissolved after 30 min (DP), T_{50} = time necessary to dissolve 50% drug, RDR = relative dissolution rate r = Coefficient of correlation; K_1, K_{HC} = release rate constants for First order and Hixson Crowell's model respectively.

ISSN: 0975-8585

Figure 1: Phase solubility diagram of NVP in 0.1 N HCl and pH 6.8

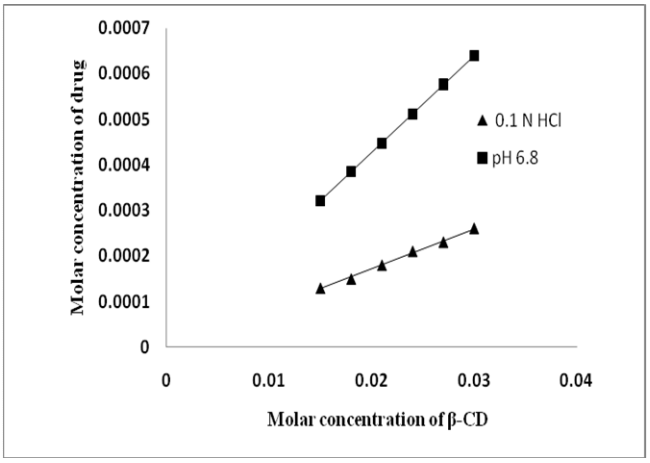
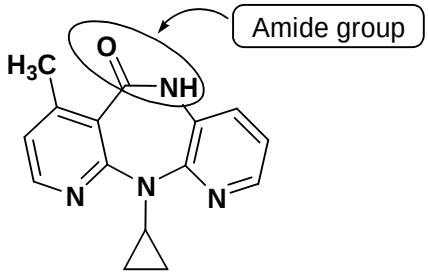


Figure 2: Chemical structure of Nevirapine

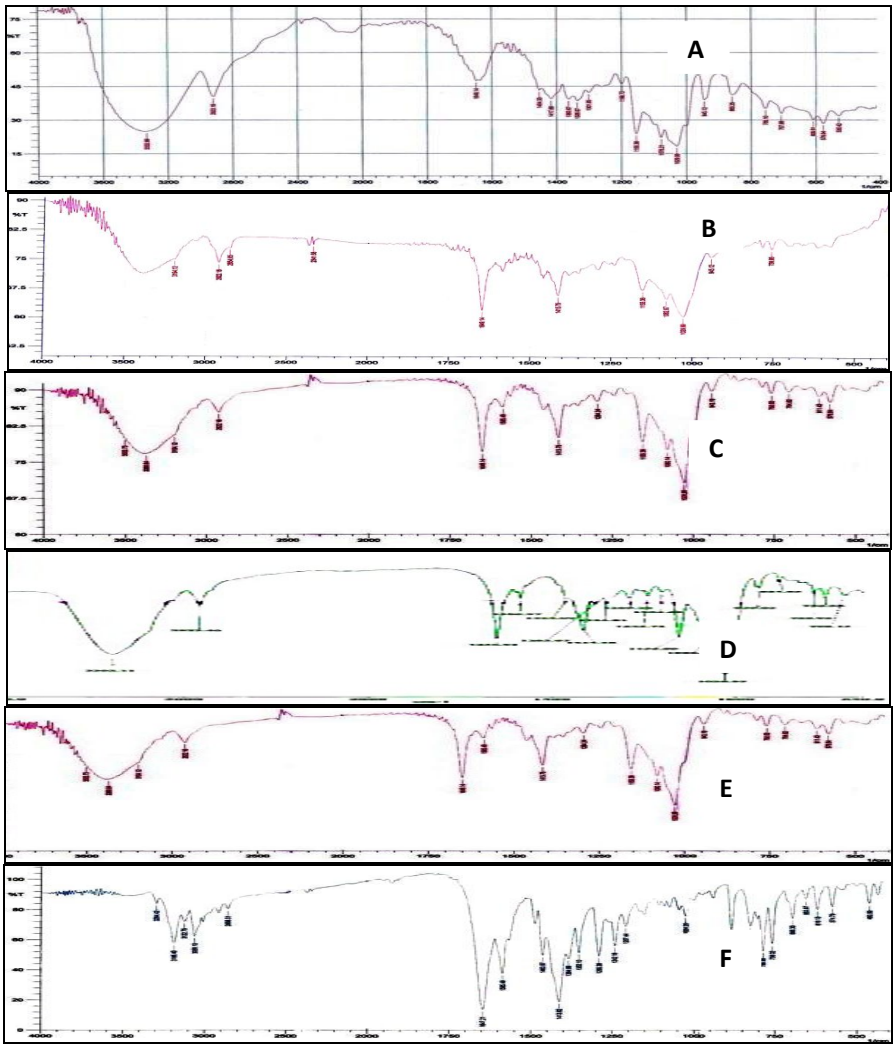


CONCLUSION

All binary systems exhibited higher dissolution rates in pH 1.2 and pH 6.8 than their corresponding physical mixtures and also the pure drug. Thus, inclusion complexes of NVP:β-cyclodextrin systems are suitable to achieve sufficient solubility along the whole gastro-intestinal tract, which is a crucial step in the development of NVP formulations. Further, the best solid binary inclusion complexes of NVP with β-CD (1:1M) can be obtained by the microwave technique ($P < 0.05$). The present results suggest that the prepared solid complexes reflect the vital role of β-CD to improve the solubility and dissolution rate of NVP both in acidic and intestinal pH via complexation process, which could minimize the variable dissolution rates with increase in oral bioavailability.

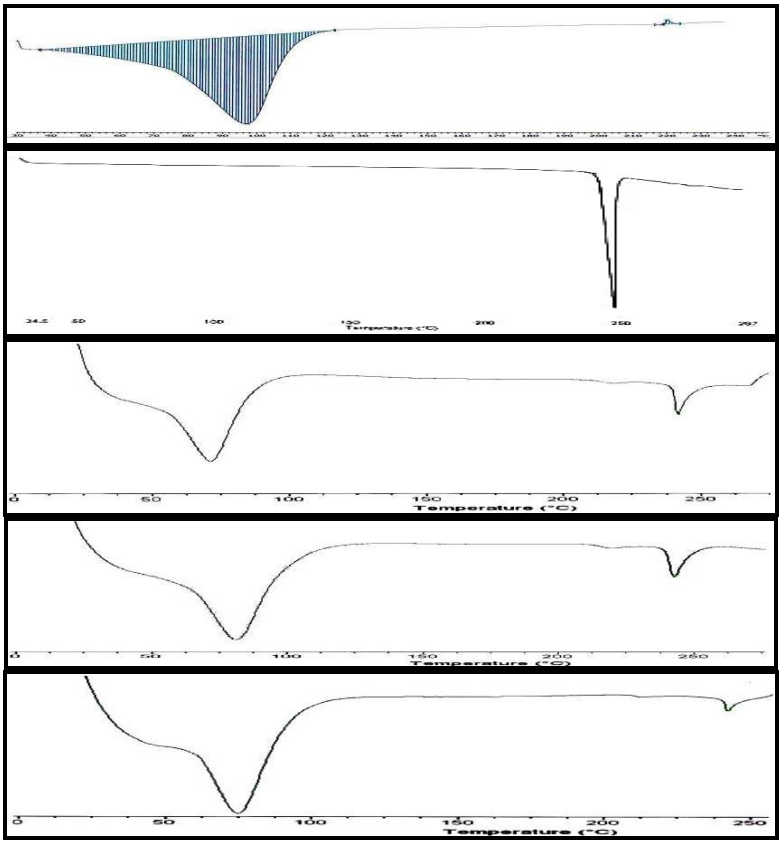
ISSN: 0975-8585

Figure 3: Comparison between FTIR spectra of (A) NVP, (B) β-CD, (C) NVP:β-CD (PM), (D) NVP:β-CD (KM), (E) NVP:β-CD (SE), (F) NVP:β-CD (MW)



ISSN: 0975-8585

Figure 4: Comparison between DSC thermograms of (A) β-CD, (B)) NVP, (C) NVP:β-CD (KM), (D) NVP: β-CD (SE) and (E) NVP: β-CD (MW)



ISSN: 0975-8585

Figure:5 Comparison between XRD spectra of (A) NVP, (B) β-CD, (C) NVP:β-CD (PM), (D) NVP: β-CD (KM), (E) NVP: β-CD (SE), (F) NVP: β-CD (MW)

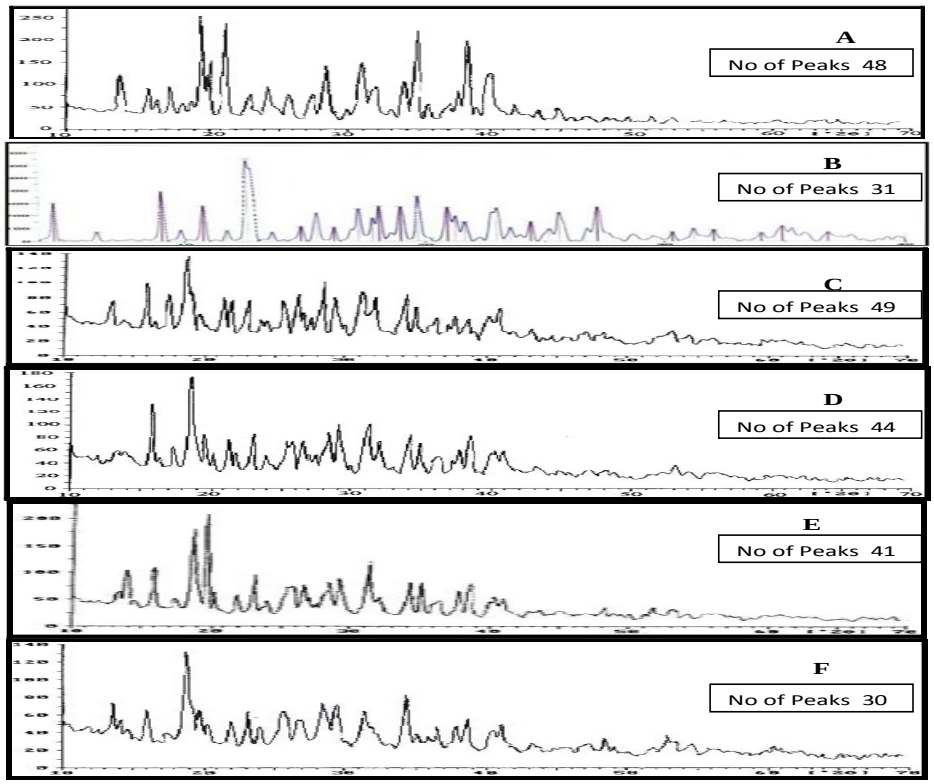


Figure 6: SEM photographs of (A) NVP, (B) β-CD, (C) NVP: β-CD, kneading method (D) NVP: β-CD, solvent method and (E) NVP: β-CD, Microwave method

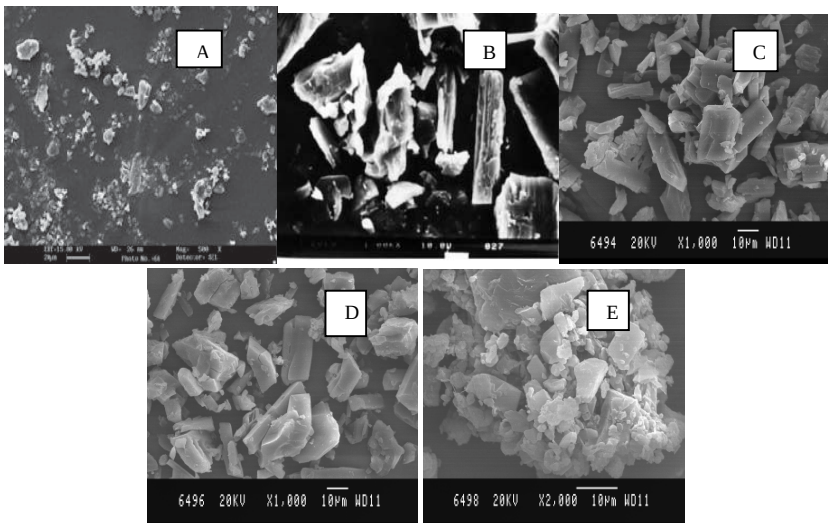


Figure 7: Comparative dissolution profiles of NVP:β-CD (1:1M) solid binary systems in 0.1 N HCl

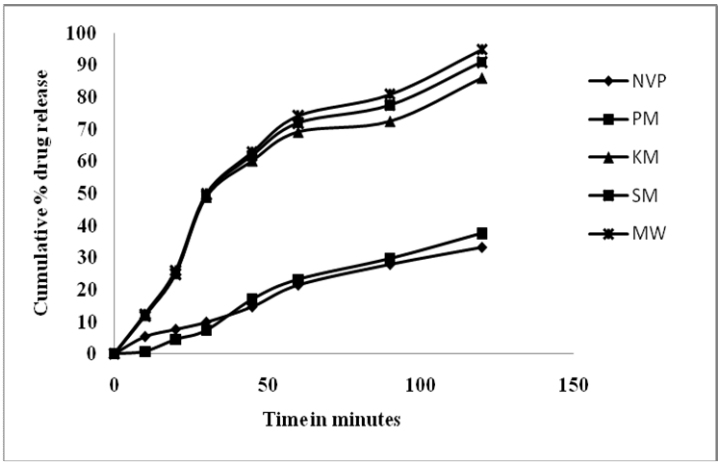
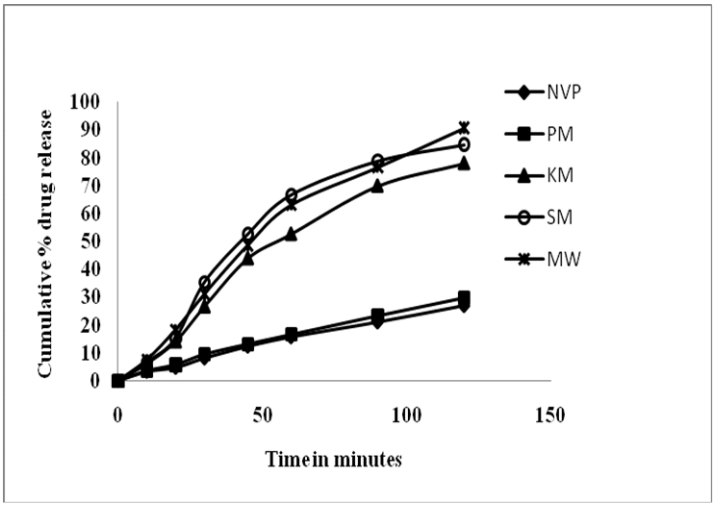


Figure 7: Comparative dissolution profiles of NVP:β-CD (1:1M) solid binary systems in pH 6.8



ACKNOWLEDGEMENTS

The authors are thankful to Academy of Medical Education, V. L. College of pharmacy, Raichur for its generous financial support to this research.

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