International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol. 3, No.1, pp 144-147, Jan-Mar 2011

Enhanced Dissolution and Spectroscopic Analysis Studies of the Inclusion Compound of Nevirapine in β-Cyclodextrin

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Abstract: Enhance the solubility of Nevirapine by complexation using β-Cyclodextrins. Physical mixture, kneading and freeze-drying methods have been utilized for complexation of Nevirapine with β-Cyclodextrins. The physicochemical characterization of Nevirapine -β-Cyclodextrins inclusion complex was performed using Ultraviolet (UV) spectroscopy, Infrared spectroscopy (IR), Phase solubility analyses experiments through a synthetic membrane in both solid and solution phase. Moreover, interactions between Nevirapine and β-Cyclodextrins were studied in DMSO by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. Phase solubility studies revealed 1:1 M complexation of Nevirapine when the freeze-drying method was used for the preparation of the inclusion complex. FT-IR and UV studies confirmed the true inclusion for the freeze-dried inclusion complex. The dissolution study revealed that the drug dissolution rate was improved by the presence of CDs and the maximum and prompt release was obtained with the freeze-dried inclusion complex.

Key words: Inclusion complex, Nevirapine, β-Cyclodextrins, IR.

Introduction

Nevirapine is chemically, 1-cyclopropyl-5, 11-dihydro-4-methyl-6H-dipyrido [3,2-b: 21,31-e] [1,4] diazepin-6-one. It is a non-nucleoside reverse transcriptase inhibitor and antiretroviral used in the treatment of AIDS .Nevirapine is official in Indian Pharmacopoeia [1]. The therapeutic effectiveness of a drug depends upon the ability of the dosage forms to deliver the medicaments to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. Some drugs having poor bioavailability are with poor aqueous solubility and or slow dissolution rate in the biological fluids. Applications of CDs in oral drug delivery include improvement of drug bioavailability due to increased drug solubility, improvement of rate and extent of dissolution and /or stability of the drug at the absorption site, reduction of drug induced irritation, taste masking, etc. ß- Cyclodextrin (ß-CD) is cyclic malto oligosaccharides in which the glucose units are linked by a- 1, 4 glycoside bonds. [2].The peculiar arrangement of the glucose units imparts the molecule a cone like structure, which makes the exterior of the cone hydrophilic and interior of the cone hydrophobic in nature. This characteristic of the polymer enables encapsulation of the drug in the cavity resulting in the improvement in the solubility, drug release as well as taste masking. They have hydrophobic central cavity and a hydrophilic outer surface [2]. CDs have been found to be very useful in enhancing the solubility of poorly water-soluble drugs owing to the formation of inclusion complex of the drug in its hydrophobic cavity [3-7]. The most common natural CDs are α Cyclodextrins, ß cyclodextrin and γ cyclodextrin, which are formed by six, seven, and eight glucose units, respectively. Apart from these naturally occurring CDs, various derivatives are also available [8-9].which may produce better solubility when a complex [10, 11] but cost and toxicity factors poses limitation in their use. In previous years Cyclodextrins

(CDs) have been recognized as important constituents of pharmaceutical excipients. They are cyclic oligosaccharides consisting of (α-1, 4)-linked α-D-glucopyranose units, with a relatively hydrophobic central cavity and a hydrophilic outer surface. The most abundant natural CDs are α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD), containing 6, 7, and 8 glucopyranose units, respectively. β-cyclodextrin (β-CD) has been used in this work. The hydrophilic exterior surface of the CD molecules makes them water-soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized nonpolar molecules.CDs are capable of forming inclusion complexes with many drugs by including a whole drug molecule, or only some non-polar part of it, inside their cavity. These noncovalent complexes show new physicochemical characteristics when compared with the guest molecules. They include better stability, higher aqueous solubility, increased bioavailability, and less undesirable side effects [12-15]. In the present study, different technique has been used to prepare inclusion complex of Nevirapine with β-cyclodextrin. Prepared inclusion complex was characterized by Infrared (IR), Ultraviolet (UV) and Nuclear Magnetic resonance (NMR) spectroscopy. The evaluation was performed by invitro dissolution, diffusion and comparing the release profile of inclusion complex with marketed formulation in two buffer solutions pH 4.0 and pH 7.4. The aim of this study was to improve the biopharmaceutical properties of Nevirapine by the formation of Nevirapine / β-cyclodextrin inclusion complex.

Materials and Method

All other chemicals were of analytical grade and used without further purifications. Measurements of pH were performed using a calibrated Elico pH meter. Nevirapine concentrations were determined at 303.6 nm using Shimadzu UVspectrophotometer. As a starting point for this study, the solubility of Nevirapine as a function of pH was studied. A series of buffer solutions from pH range 4.0 to 7.4 were prepared and Nevirapine was added in sufficient quantity to saturate each solution. To avoid change in concentration due to evaporation, the solutions were kept in vials sealed with Teflon lined screw caps and wrapped with paraffin. All solutions were then placed on a test tube rotator for mixing.

Determination of Stability Constant (K)

Complexation studies were performed according to the method reported by Higuchi. An excess amount of Nevirapine was added to the aqueous solution of various concentrations (0.02-0.008 m M/L) of ß-CD solution (molecular weight = 1135). The contents were stirred for 7 hours at 37°C ± 2°C. After equilibrium, the samples were filtered and absorbance was measured at 303.6 nm (UV/ VIS spectrophotometer, Japan).

Methods

Preparations of Solid Binary Systems

Nevirapine -β-cyclodextrin binary systems were prepared (1: 1, and 1:2 molar ratios) as described in detail below.

Physical Mixture

The required and accurately weighed amounts (equimolar) of Nevirapine and β-CD were pulverized, sieved, and homogenously mixed in a ceramic mortar.

Freeze-drying Procedure

The required stoichiometric amounts of Nevirapine and β-CDs were accurately weighed and dispersed in 15 mL of aqueous solutions until semisolid systems were obtained, which were then stored in a nitrogen atmosphere for 10 hours. Then, products were dissolved in 100 mL of distilled water and stirred under mechanical stirring for 40 minutes at 70°C-80°C. After filtration at the same temperature, the filtrate was frozen at −5°C/−15°C and then freeze dried for 48 hours at 70°C Acetone was taken, as solvent as both the drug and β-cyclodextrin were completely soluble in it.

Ultraviolet spectroscopy

The UV spectra were recorded UV-Visible spectrophotometry (shimadzu-1700) in the range 200-400 nm. Sample was run in 10 mm quartz cell with water in the reference cell. The Nevirapine and Nevirapine / β cyclodextrin samples were prepared in situ in a 5 ml cuvette. A 5 µl aliquot of a 0.5 w/v Nevirapine / 99.9% v/v ethanol solution was pipette into a cuvette containing a known volume of water (3ml). The cuvette was then stoppered and shaken. The spectrum was recorded between 200-400 nm and the absorbance measured at 303.6 nm.

Infrared Spectroscopy

Infrared spectroscopy (IR) spectra of pure Nevirapine and β-CD, as well as their binary products, were using instrument with KBr disc method. Analysis was performed at room temperature.

Evaluation of Binary Systems

Phase Solubility Studies

Phase solubility studies were performed; following the method previously described by Higuchi and Connors in solutions at pH 3.0, 5.0, and 7.4. Briefly, excess amounts of Nevirapine (200 mg) were added to 10 mL of aqueous solutions containing different concentrations of β-CD (0-5 mM). Suspensions were vigorously stirred at 37°C ± 3°C for 4 days.

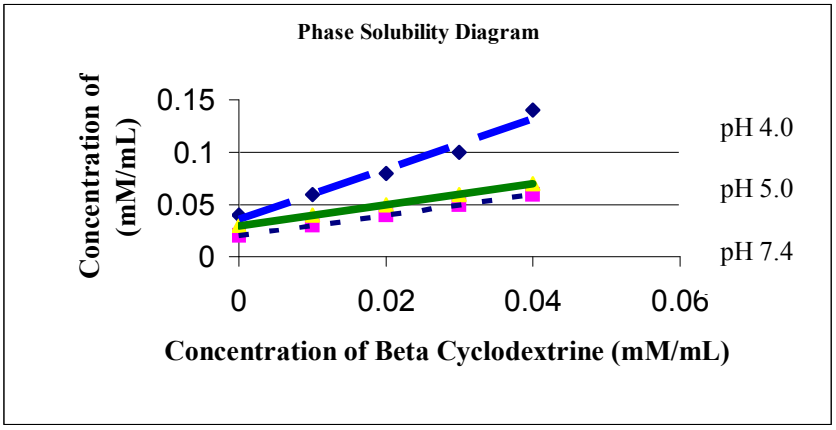

Figure. Phase solubility diagram of Nevirapine -β Cyclodextrins at different pH

Dissolution studies

The dissolution profile was studied using USP dissolution rate test apparatus employing paddle stirrer. In 900 ml dissolution medium (2 hrs using 0.1 N HCl and the medium was replaced with phosphate buffer pH 7.4), a sample of 200 mg drug equivalent complex (1:1m, 1:2m) was placed and set rpm at 800 and temperature $+37^0$ C. Aliquots of 10 ml was withdrawn at 20 mints intervals of time and replaced with the same medium and analyzed at 303.6 nm by using UV visible spectrophotometer.

Effect of polymers on the dissolution rate of Nevirapine – β-CD complex

The effect of inclusion complexation of Nevirapine in β-CD and in presence of different polymers on the dissolution profile of Nevirapine is illustrated in Fig. The dissolution profiles of the ternary systems showed an increase in the dissolution rate of Nevirapine compared to the binary system. The investigated polymers increased the dissolution rate of the drug in the order of Croscarmellose sodium, PEG 6000, Avicel pH101, HPMC, PVP K60. The increase in the dissolution rate of Nevirapine might be related to the increase of complexation efficiency and solubilizing effect of β-CD in presence of water-soluble polymers. This might indicate a sort of interaction between this polymer where many cyclodextrin molecules are threaded onto a linear polymer. Such inclusion complex formation between β-CD and polymers will reduce the ability of β-CD to form complex with the drug.

Formulation studies-

Tablets containing 200 mg of Nevirapine were prepared by direct compression using different excipients like Lactose monohydrate, colloidal silicon dioxide, and magnesium stearate. Tablets containing complexes (equivalent to 200 mg Nevirapine) prepared by kneading and co evaporation method were also prepared similarly using less quantity of lactose. The blend was compressed on a six-station single rotary machine using round-shaped, flat punches to obtain tablets having thickness 6–8 mm and hardness 12–15 kg/cm^2. The tablets were studied in 6 replicates for release profile of Nevirapine using the same method described in dissolution studies.

Gibbs free energy constant and solubility studies

These results agree with the well-established formation of soluble complexes between the water soluble polymeric carriers and poorly water-soluble drugs. Increased solubility may be due to the improved wet ability of the Nevirapine particles in aqueous solution from polymers. The values of Gibbs free energy change are an indication of the process of transfer of Nevirapine from pure water to aqueous solution of polymers.

Results and Discussion

The IR spectrum of Nevirapine, β-Cyclodextrins, and Nevirapine -β-Cyclodextrins complex (1:1 molar ratio) is shown Figure. Two carbonyl peaks at 1706 cm^{-1} and 1697 cm^{-1} characterize the spectrum of Nevirapine, respectively. A broad band at 1597.6 cm^{-1} characterizes the spectrum for β Cyclodextrins, which is due to the glycoside linkages. The spectrum for the physical mix and kneaded preparation are more or less the summation of those for the carbonyl peaks of Nevirapine at 1703cm^{-1} & 1676 cm^{-1}. It can be seen that after 15 min only 15% of pure drug and is dissolved, and even after 60 min only 55 % of the drug goes into the solution whereas in case of Nevirapine β-Cyclodextrins inclusion complex prepared by kneading method, 45 % drug was released within 10 min and almost complete release (80 % and 85%, respectively) was seen after 25min in pH 3.0. The UV spectrum for Nevirapine consists of two peaks, one at 274.2nm and other at 303.6 nm.

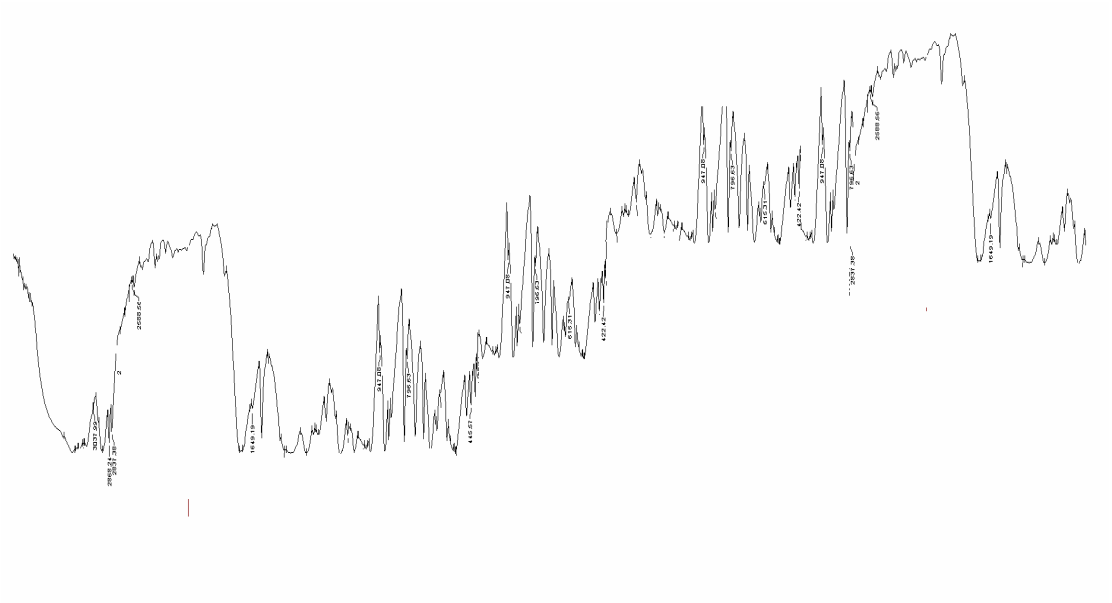

Figure-IR spectrum of Nevirapine β-Cyclodextrins inclusion complex

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