Academic Sciences

International Journal of Chemistry Research

ISSN- 0976-5689 Vol 2, Issue 3, 2011

Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION PROFILE OF NEVIRAPINE BY SOLID DISPERSION TECHNIQUE

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Received: 30 March 2011, Revised and Accepted: 02 May 2011

ABSTRACT

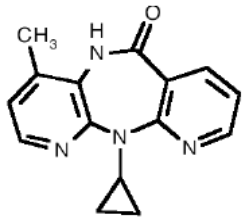
Solid dispersions (SDs) of nevirapine (NVP) were prepared with the objective of dissolution enhancement by solvent evaporation technique by using polymers like PEG 6000 and PVP (k 30). The Fourier transform-IR (FTIR) studies indicated the possibility of hydrogen bonding with the polymer. Powder-XRD and 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 and pH 6.8 phosphate buffer solution showed a significant increase in dissolution rates of NVP comparing to physical mixtures and pure drug. Comparatively, SD of NVP: PEG 6000 and NVP: PVP (K30) in various weight ratios (1:2, 1:4, 1:6) were prepared by solid dispersion method exhibited a higher release rate than the conventional method. Improved dissolution of model drug may be attributed to the modification in drug crystalline in SDs as was evident from our analytical studies. The dissolution pattern of the NVP from all the SDs followed predominantly, first order kinetics. This study reflects the vital role of polymers as a novel approach to improve the solubility of NVP, which could minimize the variable dissolution rates with increase in oral bioavailability.

Keyword: Nevirapine, Solid dispersion, Solvent evaporation, Bioavailability.

INTRODUCTION

Now days, the drugs which exist and those being discovered are of synthetic origin and have limitation of poor water solubility. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, etc[1].

Nevirapine is a drug belonging to a class of pharmacological agents known as the non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1.Chemically it is 11-cyclopropyl-4-methyl-5,11-dihydro-6*H*- dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one[2].



Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Nevirapine is used for the treatment of HIV-1 infection. Nevirapine was having extensive first pass metabolism, and relative Elimination half-life of about 45 hrs. (extended-release) and associated with frequent dosing of conventional dosage form makes it suitable candidate for sustained release dosage form for patient compliance. Compound with poor aqueous solubility are extremely challenging to be developed as new drugs. It is well known that drug dissolution rather than permeation through the epithelia of the gastro intestinal tract is responsible for a low oral absorption. One of the pharmaceutical strategies to improve the oral bioavailability is formation of solid dispersion[3-5]. Solid dispersion can able to improve their dissolution by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. In this project work, Nevirapine was selected as model drug, because it is having poor aqueous solubility and low dissolution rate[6].

In 1971 Chiou and Riegelman defined solid dispersion as "A dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent evaporation or melt solvent method". Solid dispersion when exposed to aqueous media, the carrier is dissolved; the drug is released as very fine colloidal particles[7],and widely used to increase intrinsic solubility or dissolution and further the bioavailability of drug [8-9].Various carriers can be used for solid dispersion preparation which includes polyethylene glycol, poly vinyl pyrolidone, urea, mannitol, poloxamers etc. Solid dispersion can be prepared by conventional methods such as solvent evaporation method, fusion method and melt solvent method and novel methods used for preparation includes super critical fluid technology, electros pining, spray drying, lyophilization and melt extrusion method[10].

MATERIALS

Nevirapine was kindly received as a gift sample from Aurobindo Pharma, Hyderabad. Poly ethylene glycol 6000 (PEG 6000), PVP (K30),Potassium Di-hydrogen Phosphate, Sodium hydroxide were purchased from Merck Ltd., Hyderabad, Potassium chloride, Hydrochloric acid were procure from Signet Chemical Corporation, Mumbai All other reagents used were of analytical grade.

METHODS

Preparation of solid dispersion

Solid Dispersion of Nevirapine in PEG 6000 containing three different weight ratios(1:2, 1:4, 1:6) were prepared by the solvent evaporation method. An appropriate amount of Nevirapine was added to a solution of PEG 6000 in Methanol. The solution was stirred at 25°c for 2 hours, and the solvent was removed, under vacuum at 40°c in a vacuum tray dryer (VTD) for 12 hours. The solid residue was pulverized and sieved using #40 meshes. Solid Dispersion of Nevirapine in PVP (k 30) also prepared by the above method containing three different weight ratios (1:2, 1:4, 1:6). The solid dispersions are stored in light resistant container[11].

Solubility study of solid dispersion

The individual tablet from each ratio was crushed in mortar. Then weight the SD powders from each ratio separately. Each weighted SD powders separately added in 100ml of Acid buffer pH 1.2. Then shake for 1 hour and kept for 15 minutes. From that 0.5ml solution from each ratio separately taken and make the volume up to 10ml. Then it is analyzed at 314 nm by UV spectrophotometer (table no 1-2). Each sample was analyzed in triplicate[12].

Physicochemical characterization of SDs by FT-IR, DSC and Powder XRD:

FTIR was employed to characterize the possible interaction between the drug and the carrier in the solid state on an FTIR multi scope spectrophotometer by the conventional KBr pellet method (Fig-1, 2, 3, 4, 5). The spectra were scanned over a frequency range 4000-400 cm^{-1} with a resolution of 4 $cm^{-1.}$

DSC analysis of the drug, carrier SD was carried out on the samples using DSC (Mettles). Samples (5mg) were heated under nitrogen atmosphere on an aluminum pan at a rate of 10°c/min over the temperature range of 30°c and 300°c. Thermal data analysis of DSC thermogram was conducted using STAR software (version 8.10). The thermo gram of the pure drug, PEG6000 and SD are illustrated (Fig-6, 7). The DSC thermo gram of each component exhibited a sharp endothermal peak corresponding to melting point[13].

Nevirapine shows a sharp peak at 249.04°c, PEG6000 shows at 60.40°c. The thermo gram of SD containing the Nevirapine & PEG6000 demonstrated two endothermic transactions. The first transition peak was observed very close to melting point of PEG6000 Were as the second minor transition peak at 236.60°c is corresponding to the melting temperature of the drug gradually shifted to the lower temperature, losing its sharp and distinctive appearance. This is due to the dissolution of the drug in melted carrier.

The powder XRD patterns of pure drug, physical mixtures and solid dispersions were recorded using Philips X-ray powder diffract meter (model PW1710) with Cr as anode material, operated at a voltage of 40 kV and a current of 25 mA. Samples were analyzed in the 2q angle range of 5-40° and the process parameters were set as: scan step size of 0.02° (2 q), scan step time of 0.8 s and time of acquisition of 1 h.

In vitro dissolution studies

The solubility of pure Nevirapine will be enhanced, with increasing the dissolution rate of pure Nevirapine. Base on this fact, dissolution rate of pure Nevirapine increase with increasing the various PVP (k 30) content. Since SD of Nevirapine with PVP (k 30) exhibits enhanced dissolution rate (Fig-8), it can be assumed that this may improve its rate of absorption in vivo. Possible mechanism of increased dissolution rate of SD includes: reduction of particle size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and finally the combination of previously mentioned methods. The dissolution behavior of pure Nevirapine and SD of PVP (k 30), pure Nevirapine and SD of PEG 6000, in various weight ratios(1:2, 1:4, 1:6) have been shown in terms of dissolution efficiency at 0, 15, 30, 45, 60, 90, 120 minutes (0.15, 0.30, 0.45, 0.60, 1.30, 2.00 hours) in Acid buffer pH 1.2 and Phosphate buffer pH 6.8 dissolution mediums, in USP-1(Paddle) apparatus, at time point 0, 15, 30, 45, 60, 90, 120 minutes (0.15, 0.30, 0.45, 0.60, 1.30, 2.00 hours).

Statistical analysis

Statistical analysis was performed to assess the solubility of NVP from SDs systems. The percent dissolution efficiency (DE) values obtained from dissolution studies of SDs were compared by one-way ANOVA at 95%mconfidence interval. A significance level of $P < 0.05$ was used to denote significance in all cases.

RESULTS & DISCUSSION

In the present study, the solubility characteristic of Nevirapine was observed in various types of medium. Pure Nevirapine is freely soluble in Acetone and Chloroform, sparingly soluble in Alcohol and Methanol, very slightly soluble in Water. The solubility of Nevirapine was observed in pH 1.2 and pH 6.8 buffer solutions. Than pH 6.8 ± 0.2 and pH 1.2 ± 0.2 buffer solutions was taken as a dissolution medium. The solubility of pure Nevirapine was enhanced, with increasing the dissolution rate of pure Nevirapine. Based on these facts, dissolution rate of pure Nevirapine increased, with increasing the various Polymers content. The solubility of pure Nevirapine was observed in pH 6.8 ± 0.2 and pH 1.2 ± 0.2 buffer solutions, with increasing the polymer ratios as 1:2, 1:4 and 1:6. The SD of Nevirapine with PEG 6000, and PVP (K 30) prepared successfully by solvent evaporation method in different ratio. In case of SD of Nevirapine + PVP (K30), the dissolution at Q120 is less, than the SD of Nevirapine + PEG 6000 the dissolution at Q120.

Table 1: Solubility study on solid dispersion of Nevirapine with PEG 6000

Ingredients Name	Absorbance	Conc. of drug (µg/ml)	Dilution factor	Actual conc.	Amount	% Nevirapine Present
Nevirapine + PEG6000 SD(1:2)	0.6144	22.36	20	447.26	44.72	89.40
Nevirapine + PEG6000 SD(1:4)	0.6311	22.98	20	459.77	45.97	91.90
Nevirapine + PEG6000 SD(1:6)	0.6832	24.94	20	498.8	49.88	99.70
Pure Nevirapine Tablet	0.6948	22.37	20	447.56	44.75	89.50

Table 2: Solubility study on solid dispersion of Nevirapine with PVP (K30)

Ingredients name	Absorbance	Conc. of drug (µg/ml)	Dilution factor	Actual Conc.	Amount	% Nevirapine present
Nevirapine + PVP(K30) SD (1:2)	0.6048	22.0	20	440.00	44.00	88.00
Nevirapine + PVP(K30) SD (1:4)	0.6298	22.94	20	458.80	45.88	91.70
Nevirapine + PVP(K30) SD (1:6)	0.6485	23.64	20	472.80	47.28	94.50
Pure Nevirapine Tablet	0.6948	22.37	20	447.56	44.75	89.50

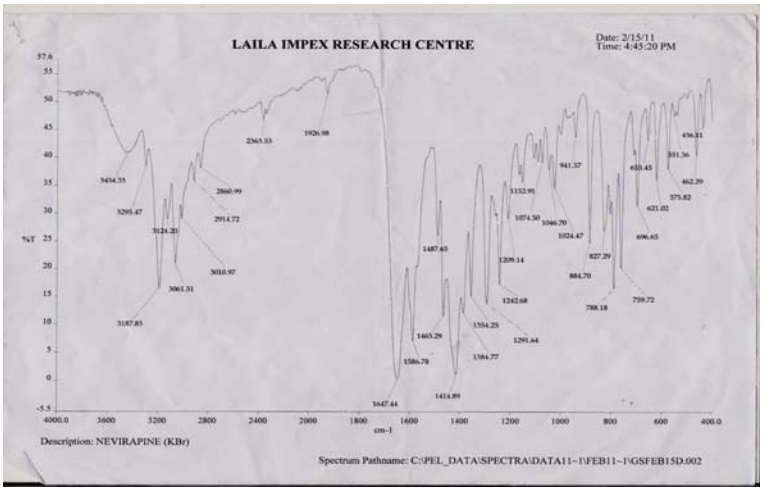


Fig. 1: FTIR Spectra of Nevirapine (NV)

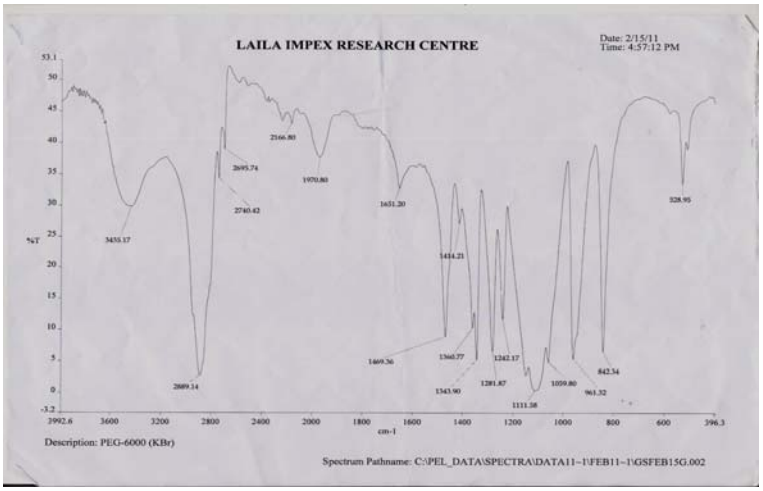


Fig. 2: FTIR Spectra of PEG-6000

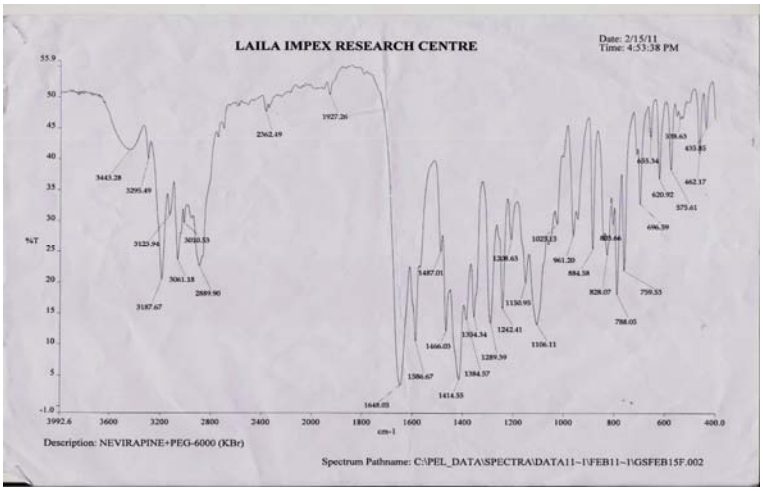


Fig. 3: FTIR Spectra of Nevirapine with PEG 6000

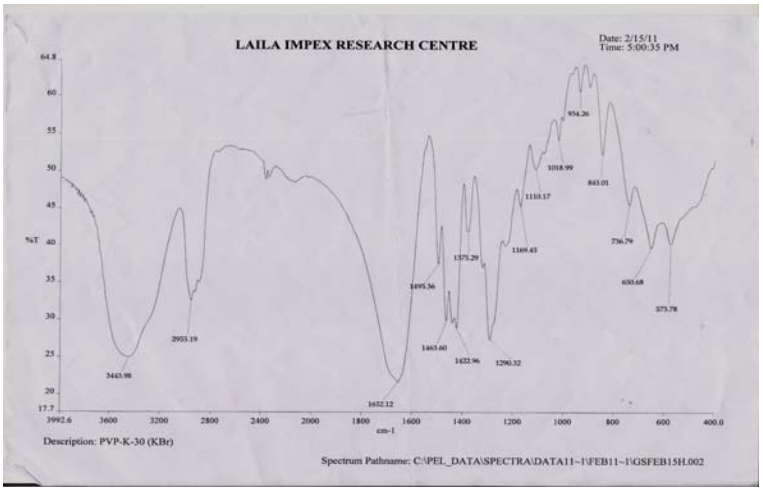


Fig. 4: FTIR Spectra of PVP (K 30)

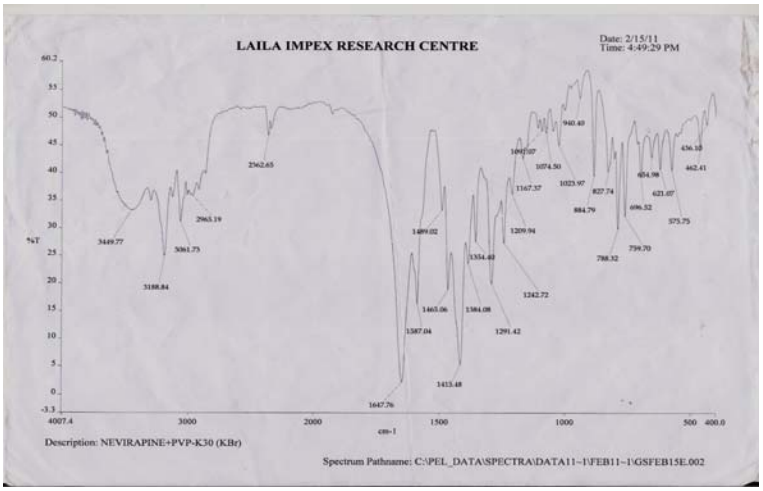


Fig. 5: FTIR Spectra of Nevirapine with PVP (K 30)

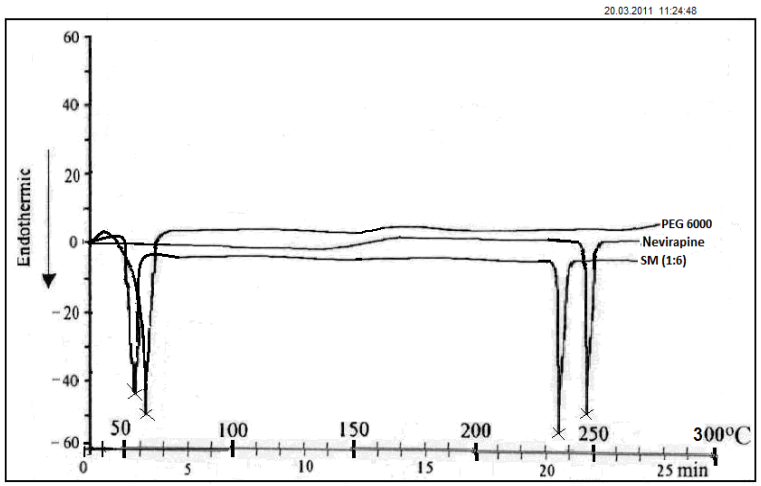


Fig. 6: DSC curve of Nevirapine (NV), PEG 6000, and Nevirapine & PEG6000 SD(SM)

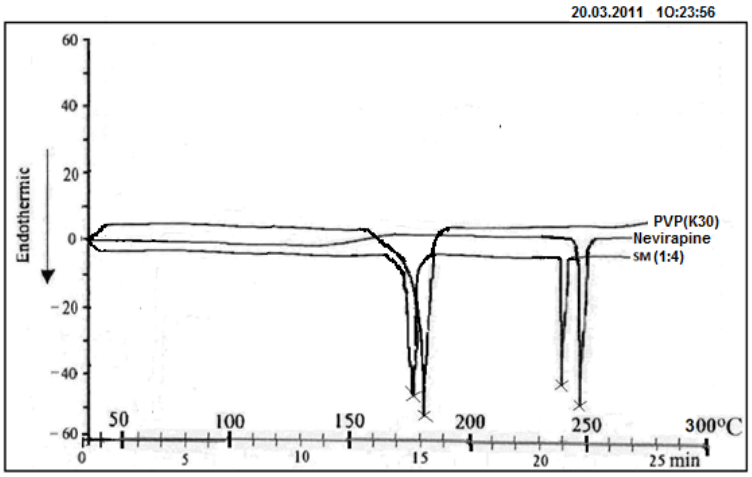


Fig. 7: DSC curve of Nevirapine (NV), PVP (K30), and Nevirapine & PVP (K30) SD(SM)

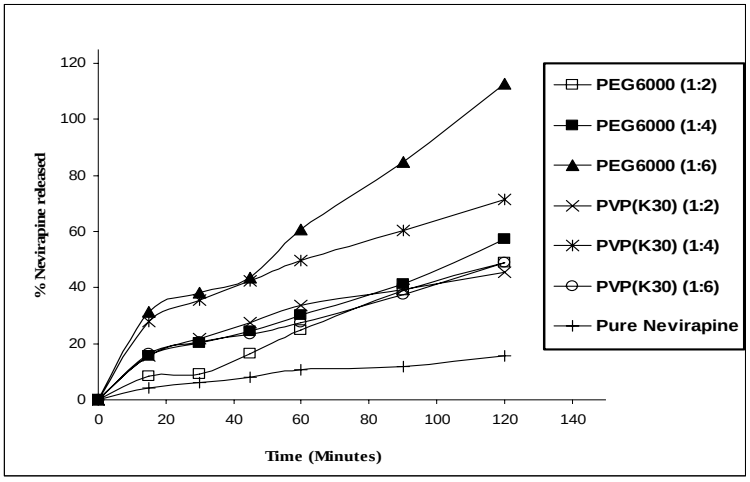


Fig. 8: Dissolution profiles of Nevirapine with PEG 6000 and PVP (K30) [in Phosphate buffer pH 6.8 solution]:

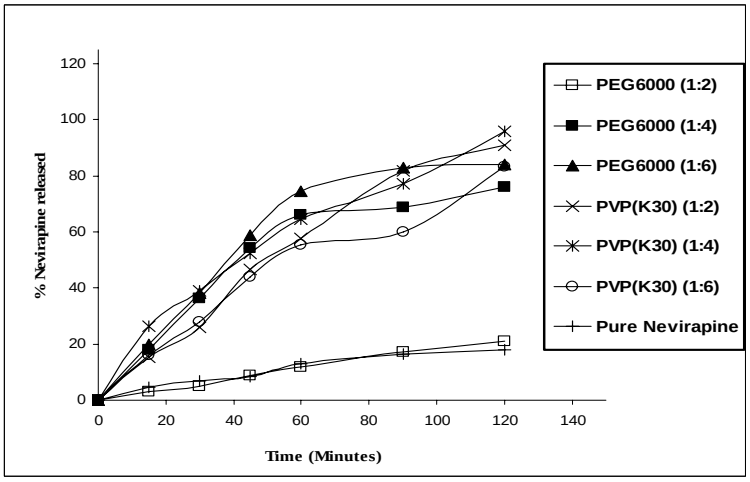


Fig. 8: Dissolution profiles of Nevirapine with PEG 6000 and PVP (K30) [in Acid buffer pH 1.2 solutions]:

In-Vitro dissolution showed that, there were increased in dissolution rate in case of SD of Nevirapine and PEG 6000 (1:6 ratio) and Nevirapine with PVP (K 30) (1:4 ratio). It was observed that complex formed between Nevirapine and PEG 6000 (1:6 ratio) and Nevirapine with PVP (K 30) (1:4 ratio) had change the structure of the drug. Solid Dispersion of Nevirapine in PEG 6000, and PVP (K 30) improved the dissolution rate of Nevirapine, which helps to enhancing solubility of Nevirapine. The relative dissolution potency of the carrier might be ranked as PEG 6000 > PVP (K 30). Effects of the preparation methods and the mixing ratios on the dissolution were clearly observed. DSC curve of Nevirapine showed an endothermic peak at 249.04°c. DSC curve of PEG 6000 with SD of Nevirapine (1:6 ratio) and PVP (K30) + SD of Nevirapine (1:4 ratio) was established, where PEG 6000 showed a endothermic peak at 60.40°c and PVP(K30) showed a endothermic peak at 181.40°c. Solid Dispersions of PEG 6000 with Nevirapine (1:6 ratios) and PVP (K30) with Nevirapine (1:4 ratio) can be selected for future capsules or tablets formulations.

CONCLUSION

All SDs exhibited higher dissolution rates than their corresponding physical mixtures and also the pure drug. These findings are extremely important from a commercial point of view, as the prepared Solid Dispersion formulation, removes a major draw back for Nevirapine in therapy.

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