Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 2 Issue 12 December 2018

Research Article

Cosolvents and Surfactants as Potential Vehicles or Co-vehicles in Nevirapine Liquid Formulation: Pharmacokinetics Study

CJ Mbah*, NJ Nwodo and LN Umegbo

Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria

***Corresponding Author:** CJ Mbah, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria.

Received: September 28, 2018; **Published:** November 30, 2018

Abstract

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used for prophylaxis and treatment of human immunodeficiency virus (HIV) infections.

The purpose of this study was to investigate the appropriateness of using cosolvents (glycerol, propylene glycol) and surfactants (polysorbate-80, sodium lauryl sulfate) as vehicles or co-vehicles in liquid pharmaceutical dosage formulations of nevirapine by studying their effects on the pharmacokinetic parameters of nevirapine in rats.

A single dose of nevirapine was administered orally (25 mg/kg) to rats in 20% w/v cosolvent and 1% w/v surfactant solution respectively.

The area under the plasma concentration-time curve ($AUC_{0-\infty}$) and the peak plasma concentration (C_{max}) of nevirapine were increased significantly ($p < 0.05$) by both vehicles. The relative bioavailability (RB) of nimodipine was 2.2-fold and 2.5-fold greater for propylene glycol and sodium lauryl sulfate respectively than the control group.

Based on some pharmacokinetic parameter data, the enhanced oral bioavailability of nevirapine might be mainly due to inhibition of the drug metabolism by cytochrome P450 of which nevirapine is a substrate. The study suggests that cosolvent (glycerol or propylene glycol) and/or surfactant (polysorbate-80 or sodium lauryl sulfate) could be appropriate to be incorporated into liquid pharmaceutical dosage formulations containing nevirapine.

Keywords: Cosolvents; Surfactants; Pharmacokinetics; Nevirapine

Introduction

Nevirapine is chemically defined as 11- cyclopropyl-4-methyl-5,11- dihydro-6H-dipyrido {3,2-b:2',3'-e} {1,4} diazepine- 6-one. The chemical structure is presented in figure 1.

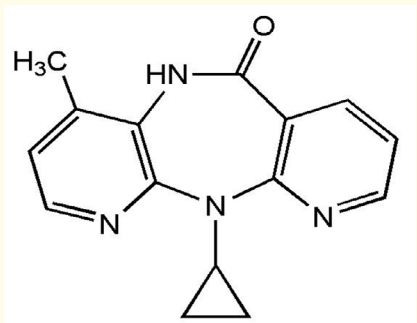

Figure 1: Chemical structure of nevirapine.

The drug is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and structurally a member of the dipyrido - diazepinone chemical class of compounds. In clinical practice, it is used for prophylaxis and treatment of human immunodeficiency virus (HIV) infections [1,2]. It reversibly inhibits the activity of HIV-1 reverse transcriptase, an enzyme which directs the polymerization of DNA from viral RNA, a necessary component for HIV-1 replication [3]. Nevirapine binds directly to the reverse transcriptase at amino acid residues 181 and 188 thereby blocking the RNA-dependent and DNA-dependent DNA polymerase activities resulting in the disruption of the enzyme's catalytic site [4]. Nevirapine is practically

insoluble in water, has logarithm partition coefficient (octanol-water) of 2.5. The pharmacokinetics of nevirapine shows that the drug has average bioavailability greater than 90%, a 60% protein binding after a single dose. It is extensively metabolized by cytochrome P450 enzymes, with very small amount of unchanged drug excreted in urine. Nevirapine is available as tablets and oral suspensions respectively [2,5]. However, the drug could be formulated into liquid pharmaceutical dosage forms such as oral and parenteral solutions respectively.

These pharmaceutical solutions often times contain glycerol, ethanol, propylene glycol, polyethylene glycol 400 respectively or mixtures of two or more of the aforementioned alcohols as cosolvents. Likewise surfactants, mostly polysorbate-80 or sodium lauryl sulfate are also found in these pharmaceutical solutions.

Cosolvents are organic compounds found to be substantially miscible with water. They cannot interact strongly with water because of small hydrocarbon regions. This property tends to reduce the ability of the aqueous system to squeeze out non-polar solutes [6,7].

Surfactants are amphiphilic molecules composing of a hydrophilic polar moiety (head) and a hydrophobic non-polar moiety (tail). They form colloidal-sized clusters in solutions, called micelles. Micelles have anisotropic water distribution within their structure hence micellar core solubilizes non-polar molecules, while compounds with intermediate polarity tend to be distributed along the surfactant molecules in certain intermediate positions.

These vehicles or co-vehicles are incorporated into pharmaceutical dosage forms to improve bioavailability and efficacy of pharmaceutical active ingredients. Previous studies [8,9] have shown that cosolvents and/or surfactants have significantly enhanced bioavailability of drugs by inhibiting their metabolism. Therefore, it was considered of interest to investigate the potential utilization of cosolvents and/or surfactants as vehicles or co-vehicles in liquid pharmaceutical dosage formulations of nevirapine while envisaging inhibition of the drug metabolism. This was carried out by studying their effects on the pharmacokinetic parameters of nevirapine in rat. These parameters act as indicators of drug metabolism. Literature review has shown little or no such study.

Materials and Methods

Materials

Nevirapine (Boehringer Ingelhem, USA), glycerol, propylene glycol, polysorbate-80 (Tween 80) and sodium lauryl sulfate were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Acetonitrile and methanol were purchased from Fisher Scientific (USA). All other chemicals were reagent grade. The apparatus used included HPLC (Model LC-10A, Shimadzu, Japan) operational with quaternary pump, Rheodyne injector fitted with 20 µl loop, variable wavelength UV/Vis detector (Kratos 780, USA), Hypersil column (C_{18}, 250 × 4.6 mm, 5 µm particle size) a vortex mixer (Fisher Scientific USA) and a centrifuge 800(Techmel and Techmel, USA).

Methods

Pharmacokinetic study

Wistar male rats weighing 200 - 250g were purchased from the Faculty of Veterinary Medicine, University of Nigeria, Nsukka. The rats were allowed access to a commercial rat diet and tap water *ad libitum*. The animals were kept three per cage and maintained at room temperature (25 ± 2°C and 50 - 60% relative humidity. The rats were strictly handled in accordance with the ethics regulations of Faculty of Veterinary Medicine Animal Care Committee in terms of welfare and experimental procedures. The animals were fasted for 12h with free access to water prior to the experiments, and each rat was anesthetized with diethyl ether.

They were divided into five groups (n = 3). Groups 1 to 4 received nevirapine dissolved in 20% w/v cosolvent solutions (glycerol-water mixture, propylene glycol-water mixture) and 1% w/v surfactant solutions (polysorbate-80, sodium lauryl sulfate) respectively. Group 5 (control) received nevirapine dissolved in distilled water. Nevirapine (25 mg/kg) was administered intragastrically using a feeding tube. A 0.5 ml of blood was collected into EDTA tubes from the orbital plexus of the rat at 0 (to serve as control) 1, 2, 3, 4, 6, 8, 12h after nevirapine administration. The blood samples were properly mixed and centrifuged at 5000 rpm for 15 min. The separated plasma samples were analyzed immediately or stored at -21°C until HPLC determination.

HPLC determination

The plasma sample was allowed to thaw at room temperature. The precipitation of plasma protein from drug sample was done by

adding acetonitrile: methanol mixture (4:1). The mixture was vortex for 10 min and centrifuged at 5,000 rpm for 15 min. Nevirapine content in the separated clear supernatant liquid was analyzed by HPLC. A 10 µl of the supernatant was injected into the chromatograph. The UV detector was set a wavelength of 250 nm. The mobile phase which consisted of acetonitrile and water mixture (70:30 v/v) was filtered through a 0.45-µm pore size membrane filter. The flow rate was 1.0 ml/min. The concentration of unknown in plasma samples was calculated from the previously constructed calibration curve. The curve was obtained by plotting the peak area of nevirapine versus the concentration of the reference drug in the spiked plasma. The reference drug concentrations range was 2 - 10 µg/ml.

Results and Discussion

Least squares regression analysis of the calibration curve gave correlation coefficient (r^2) of 0.9995 over the concentration range of 2 - 10 µg/ml. No interfering endogenous compound peaks eluting at the retention time of nevirapine for blank rat plasma.

Table 1 and figure 2 respectively show the results of the cosolvent effect on the pharmacokinetics of nevirapine in rat.

Parameters	Water	Glycerol	Propylene glycol	Polysorbate-80	Sodium lauryl sulfate
C_{max} (µg/ml)	3.7 ± 0.23	4.9 ± 0.36	7.8 ± 0.27	7.0 ± 0.15	10.2 ± 0.31
T_{max} (h)	4	4	4	4	4
AUC→12h (µg.h/ml)	17.5 ± 0.37	24.9 ± 0.42	33.6 ± 0.15	27.6 ± 0.26	36.3 ± 0.47
AUC→∞ (µg.h/ml)	80.0 ± 3.3	141.0 ± 2.2	178.2 ± 5.3	140.8 ± 1.5	196.8 ± 4.2
Kelm (h^{-1})	0.224 ± 0.02	0.182 ± 0.01	0.193 ± 0.01	0.201 ± 0.03	0.189 ± 0.01
$t_{1/2}$ (h)	3.1	3.8	3.6	3.4	3.7
Cl_T (L.h/kg)	0.329 ± 0.02	0.204 ± 0.01	0.135 ± 0.04	0.157 ± 0.01	0.102 ± 0.02
Vd (L/kg)	1.47 ± 0.08	1.12 ± 0.12	0.702 ± 0.06	0.782 ± 0.07	0.537 ± 0.03
MRT (h)	4.5	5.5	5.2	5.0	5.3
% RB	100	180	220	180	250

Table 1: Pharmacokinetic Parameters of nevirapine in rats after oral administration of 25 mg/kg.

Values are: Mean ± SD (n: 3); AUC→12h: Area under the plasma concentration-time curve from 0h to 12h; AUC→∞: Area under the plasma concentration-time curve from 0 h to infinity; C_{max}: Peak plasma concentration; T_{max}: Time to reach peak plasma concentration; $t_{1/2}$: Terminal half-life; Cl_T: Total body clearance; V_d: Volume of distribution; MRT: Mean residence time; % RB: Percent relative bioavailability.

The results show that glycerol and propylene glycol respectively increased the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC→∞) of nevirapine when compared with the control. Both cosolvents slightly decreased the elimination rate constant whereas the half-life was slightly increased when compared with the control. It was also observed that the steady-state volume of distribution and total clearance of nevirapine were significantly decreased by both cosolvents. In general, propylene glycol was found to display greater effect on these pharmacokinetic parameters.

The influence of surfactants on the pharmacokinetics of the drug, are given in table 1 and figure 3 respectively. The two surfactants (polysorbate-80 and sodium lauryl sulfate respectively) increased the maximum plasma concentration, area under the plasma concentration-time curve (AUC→∞) of nevirapine when compared with the control. Likewise, both surfactants slightly de-

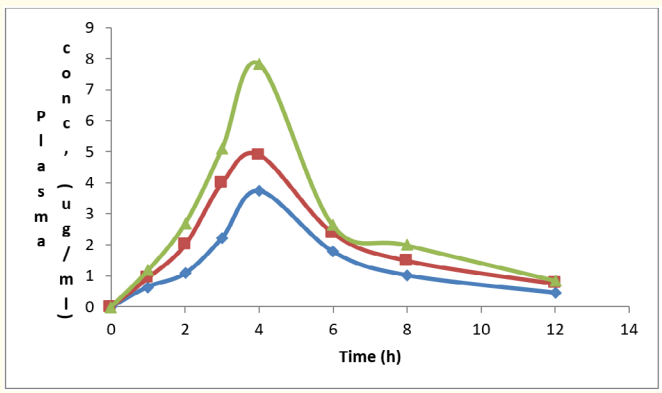

Figure 2: Plot of plasma concentration (µg/ml) versus time (hour) - effect of cosolvents.

□--------□: Control
□------□: Glycerol
Δ------Δ: Propylene glycol.

creased the elimination rate constant and increased the half-life of the drug. The steady-state volume of distribution and total clearance were significantly decreased by both surfactants when compared with the control. Sodium lauryl sulfate gave greater effect on the pharmacokinetics of nevirapine than polysorbate-80.

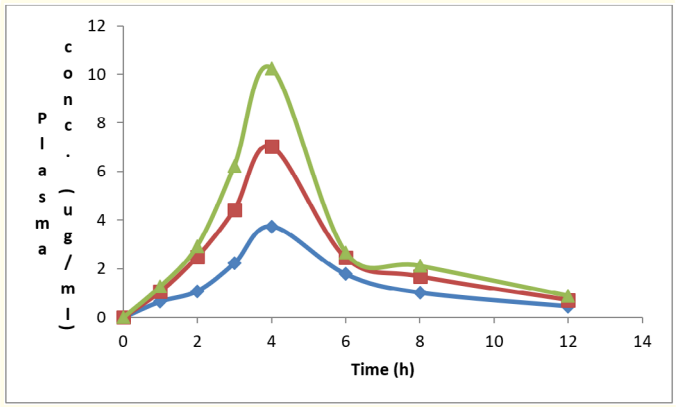

Figure 3: Plot of plasma concentration (µg/ml) versus time (hour) - effect of surfactants.

□--------□: Control
□------□: Polysorbate-80 (Tween 80)
Δ------Δ: Sodium lauryl sulfate.

These vehicles were chosen because of their utility in the formulation of liquid or solid pharmaceutical dosage forms. In addition, the concentration of cosolvent or surfactant used in the present study has been clinically employed in the formulation of these pharmaceutical dosage forms. The pharmacokinetic parameters of nevirapine were evaluated by utilizing non-compartmental pharmacokinetic model. Nevirapine maximum plasma concentration (C_{max}) and the time to reach Cmax (T_{max}) were obtained from the plot of plasma drug concentration versus time. The area under the drug concentration-time curve and mean residence time (MRT) were calculated using the trapezoidal rule. Total clearance (CLtotal) was estimated as dose (25 mg/kg)/$AUC_{0\rightarrow\infty}$ while volume of distribution at a steady state (Vss) as CLtotal × MRT. Elimination half-life (t½) was gotten following the division of 0.693 by the elimination-rate constant Ke (CL_{total}/V_{ss}).

Cosolvents and surfactants when compared with the control group, significantly ($p < 0.05$) increased the (C_{max}) and (AUCAUC→∞) of nevirapine. The increase in peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC→∞) by the studied vehicles showed that the bioavailability of nevirapine could be enhanced by cosolvency and micellization. Snawder., *et al*. [10] and Mountfield., *et al*. [11] had previously reported that propylene glycol and polysorbate 80 (Tween 90) could enhance pharmacokinetic features (such as bioavailability) of drugs by inhibiting cytochrome P450. Reduction of the total body clearance and decrease in elimination rate constant in this study could be indicators of inhibition of cytochrome P450 by the studied vehicles.

When compared with the control, the relative bioavailability (RB) of nevirapine are 1.8, 2.2, 1.8 and 2.5-fold increase for glycerol-water mixture, propylene glycol-water mixture, polysorbate-80-water mixture and sodium lauryl sulfate-water mixture respectively.

Conclusion

Cosolveny and micellization significantly enhanced the oral bioavailability of nevirapine probably by cytochrome P450 inhibition as elimination rate constants and half-lives were found to decrease and increase respectively when compared with the control. Therefore, the investigation suggests that it is appropriate to employ any of the studied cosolvents and/or surfactants as vehicles or co-vehicles in liquid pharmaceutical dosage formulations of nevirapine.

Bibliography

1. Moura MGD., *et al*. "Oral adverse effects due to the use of nevirapine". *Journal of Contemporary Dental Practice* 9.1 (2008): 84-90.

2. Adikwu E., *et al*. "Concentration-effect, incidence and mechanism of nevirapine hepatotoxicity". *American Journal of Pharmacology and Toxicology* 8.1 (2013): 20-30.

3. Umoren EB., *et al*. "Morphology of the small intestine of albino wistar rats following long term administration of nevirapine". *Biochemistry and Pharmacology* 3 (2014): 132-136.

4. Physician desk reference. 59th Edition, Thomson PDR, New Jersey (2005): 2216.

5. Beale JM in Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, edited by Block JH.; Beale (Jr) JM, 11th edition, Lippincott Williams and Wilkins, New York (2004): 393.

6. Li P., *et al*. "Combined effect of cosolvent and cyclodextrin on solubilization of non-polar drugs". *Journal Pharmaceutical Science* 88.11 (1999): 1107-1111.

7. Ran Y., *et al*. "Solubilization of cyclosporin A". *AAPS Pharmacetical Science Technology* 2.1 (2001): 2.

8. Walters KM., *et al*. "Effect of propylene glycol on the disposition of Dramamine in the rabbit". *Drug Metabolism Disposition* 21.2 (1993): 305-308.

9. Zhang H., *et al*. "Commonly used surfactant, Tween 80, improves absorption of p-glycoprotein substrate, digoxin in rats". *Archives of Pharmacal Research* 26.9 (2003): 768-772.

10. Snawder JE., *et al*. "The effect of propylene glycol on the P450-dependent metabolism of acetaminophen and other chemicals in subcellular fractions of mouse liver". *Life Science* 52.2 (1993): 183-189.

11. Mountfield RJ., *et al*. "Potential inhibitory effects of formulation ingredients on intestinal cytochrome P450". *International Journal Pharmaceutics* 211.1-2 (2000): 89-92.

Volume 2 Issue 12 December 2018

© All rights are reserved by CJ Mbah*., et al.*