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Research Article

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Pharmacokinetic Features of Nimodipine: Effects of Cosolvents and Surfactants

CJ Mbah[1], NL Umegbo[2*] and NJ Nwodo[2]

[1]Department of Pharmaceutical and Medicinal Chemistry,University of Nigeria, Nigeria
[2]Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria

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ABSTRACT

Nimodipine can be used to treat conditions such as aneurysms, subarachnoid hemorrhage, acute myocardial infarction, arrhythmia, hypertension, congestive heart failure, hypertrophic cardiomyopathy, vasospastic angina and Prenzmetal's angina. The purpose of this study was to investigate the effects of cosolvents and surfactants on the pharmacokinetics of nimodipine in rats. A single dose of nimodipine was administered orally (15 mg/kg) to rats in 20 % w/v cosolvent and 1 % w/v surfactant solution respectively. Compared with the control group, the area under the plasma concentration-time curve (AUC0-∞) of nimodipine and the peak plasma concentration (Cmax) were increased significantly ($p<0.05$) by both vehicles. The relative bioavailability (RB) of nimodipine was 2.4- fold and 3.4- fold greater than that of the control group for propylene glycol and sodium lauryl sulfate respectively. The enhanced oral bioavailability of nimodipine might be mainly due to inhibition of the CYP3A-mediated metabolism of nimodipine in the small intestine and/or in the liver and due to reduction of the total body clearance. The study suggests that cosolvent (glycerol or propylene glycol) and/or surfactant (polysorbate-80 or sodium lauryl sulfate) could be incorporated into pharmaceutical formulations containing nimodipine.

Keywords: Nimodipine; Pharmacokinetics; Cosolvent; Surfactant

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INTRODUCTION

dimethyl–4–(3–nitro phenyl) 3, 5- pyridine-dicarboxylate is a dihydropyridine calcium channel blocker with selectivity for cerebral blood vessels. Clinically, it is used in the prevention and treatment of ischemic neurological disorders caused by spasm of cerebral blood vessels following subarachnoid hemorrhage, other cerebrovascular disorders such as stroke which is associated with biological rhythm [1-3].

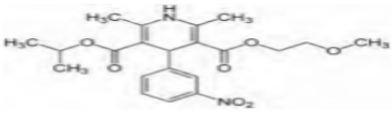

Figure 1: Chemical structure of nimodipine

The drug is practically insoluble in water. Presently it is marketed as tablets, oral solutions and intravenous infusions [4]. Oral solution could be considered dosage form of choice than solid dosage form for patients who find it difficult or are unable to swallow, such as geriatric or unconscious patients. The oral solution might 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 oral solutions.

These chemical compounds are incorporated into pharmaceutical dosage forms to improve bioavailability and efficacy of the active ingredients.

Cosolvents are organic compounds found to be substantially miscible with water. They have small hydrocarbon regions (nonpolar) and cannot interact strongly with water. This property tends to reduce the ability of the aqueous system to squeeze out nonpolar solutes [5,6].

Surfactants being amphiphilic molecules are composed of a polar moiety (hydrophilic) termed the head and a nonpolar moiety (hydrophobic) known as tail.

They form colloidal-sized clusters in solutions, called micelles. These micelles have an anisotropic water distribution within their structure hence nonpolar molecules will be solubilized in the micellar core, while compounds with intermediate polarity tend to be distributed along the surfactant molecules in certain intermediate positions.

Nimodipine oral dosage forms have excellent gastrointestinal tract absorption but it has very low systemic bioavailability due to extensive first-pass hepatic metabolism from the portal circulation thus resulting in limited clinical efficacy. The implication is that any bioavailability enhancement of such drugs could be as a result of inhibition of cytochrome P450 metabolism and/or p-glycoprotein efflux transporter. Previous studies [7, 8] have shown that pharmaceutical excipients including cosolvents and surfactants have significantly enhanced bioavailability of drugs by inhibiting their metabolism. Within this context, the present study examines the potential inhibitory effect of cosolvency and micellization on the pharmacokinetics of nimodipine in rat as literature review has shown little or no such study.

MATERIALS AND METHODS

Materials

Nimodipine, 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 (C18, 250 × 4.6 mm, 5 µm particle size) a vortex mixer (Fisher Scientific USA) and a centrifuge 800(Techmel & Techmel, USA).

Methods

Pharmacokinetic study: Health male rats weighing 220–250 g were purchased from the Faculty of Veterinary Medicine, University of Nigeria, Nsukka and were given 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 welfare of the rats and experimental procedures were strictly in accordance with the ethics regulations of Faculty of Veterinary Medicine Animal Care Committee. The rats were fasted for 12 h with free access to water prior to the experiments, and each rat was anesthetized with diethyl ether.

The rats were divided into five groups (n=3). Groups 1 to 4 received nimodipine 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 nimodipine dissolved in distilled water. Nimodipine (15 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), 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 h after nimodipine administration. The blood samples were properly mixed and centrifuged at 5000 rpm for 15 min. The separated plasma samples were stored at –21°C until HPLC determination.

HPLC determination: The plasma sample was allowed to thaw at room temperature and the plasma protein was precipitated from drug sample by adding acetonitrile: methanol mixture (4:1). The mixture was vortex for 10 min and centrifuged at 5,000 rpm for 15 min. The drug 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 230 nm. The mobile phase which consisted of acetonitrile and phosphate buffer (60:40 v/v) adjusted to pH of 3.4 with phosphoric acid was filtered through a 0.45-µm pore size membrane filter. The flow rate of 1.0 ml/min was utilized. 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 nimodipine versus the concentration of the reference drug in the spiked plasma. The reference drug concentrations are 10, 20, 30, 40, 50, and 100 ng/ml. Linear regression analysis was done.

RESULT

There were no interfering endogenous compound peaks eluting at the retention time of nimodipine for blank rat plasma.

Least squares regression analysis of the calibration curve gave correlation coefficient (r2) of 0.9985 over the concentration range of 10–100 ng/mL.

The results of the cosolvent effect on the pharmacokinetics of nimodipine in rat are given in Table 1 and Figure 2 respectively.

Table 1: Pharmacokinetic Parameters of nimodipine in rats after oral administration of 15 mg/kg

Parameters	Water	Glycerol	Propylene Glycol	Polysorbate-80	Sodium lauryl Sulfate
C_{max}(ng/mL)	87.4 ± 16	103.9 ± 14	124.8 ± 11	133.54 ± 09	179.94 ± 12
T_{max}(h)	1	1	1	1	1
AUC→12 h (ng.h/mL)	51.7	125.3	143.3	156.6	197.2
AUC→∞ (ng.h/mL)	530.5 ± 67	855.5 ± 75	1267.3 ± 79	1057.8 ± 89	1827.0 ± 92
Ke (h^{-1})	0.1004 ± 0.03	0.1487 ± 0.02	0.1149 ± 0.04	0.1504 ± 0.05	0.1100 ± 03
$t_{1/2}$ (h)	6.90 ± 1.4	4.66 ± 0.76	6.03 ± 1.1	4.61 ± 1.3	6.30 ± 0.87
Cl_T(mL.h/kg)	5.94 ± 1.2	3.68 ± 0.3	2.49 ± 0.08	2.98 ± 0.4	1.72 ± 0.2
Vd(mL/kg)	59.16 ± 2.3	24.75 ± 1.8	21.67 ± 1.7	19.81 ± 2.1	15.64 ± 1.5
MRT (h)	9.96 ± 0.04	6.73 ± 0.07	8.70 ± 0.05	6.65 ± 0.03	6.65 ± 0.03
% RB	**100**	**161**	**239**	**199**	**344**

Values are: Mean ± SD (n=3); AUC®∞=Area under the plasma concentration-time curve from 0 h to infinity; Cmax: Peak plasma concentration; Tmax: Time to reach peak plasma concentration; t1/2: Terminal half-life; ClT: Total body clearance; Vd: 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 (Cmax) and area under the plasma concentration-time curve (AUC®∞) of nimodipine when compared with the control. Both cosolvents slightly increased the elimination rate constant whereas the half-life was slightly decreased when compared with the control. It was also observed that the steady-state volume of distribution and total clearance of nimodipine were decreased by both cosolvents. In general, propylene glycol was noted to exhibit greater effect on these pharmacokinetic parameters.

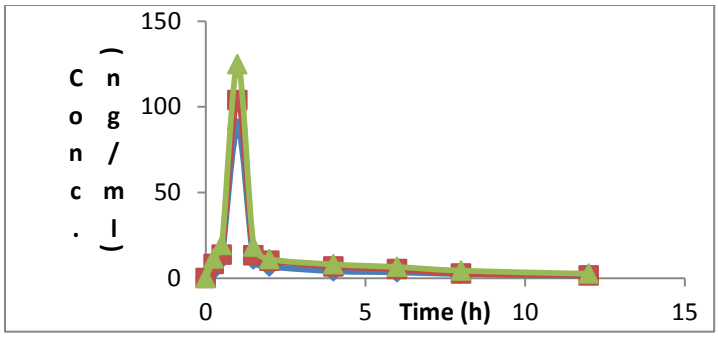

Figure 2: Plasma-concentration curve of nimodipine
□--------□ Control
□------□ Glycerol
Δ------Δ Propylene glycol

The effect of surfactants on the pharmacokinetics of the drug, are also presented in Table 1 and Figure 3 respectively. The two surfactants namely polysorbate-80 and sodium lauryl sulfate respectively increased the maximum plasma concentration, area under the plasma concentration-time curve (AUC®∞) of nimodipine when compared with the control. Similarly, both surfactants slightly increased the elimination rate constant and decreased the half-life of the drug. The results also showed that the steady-state volume of distribution and total clearance were decreased by both surfactants when compared with the control. Sodium lauryl sulfate gave greater effect on the pharmacokinetics of nimodipine than polysorbate-80.

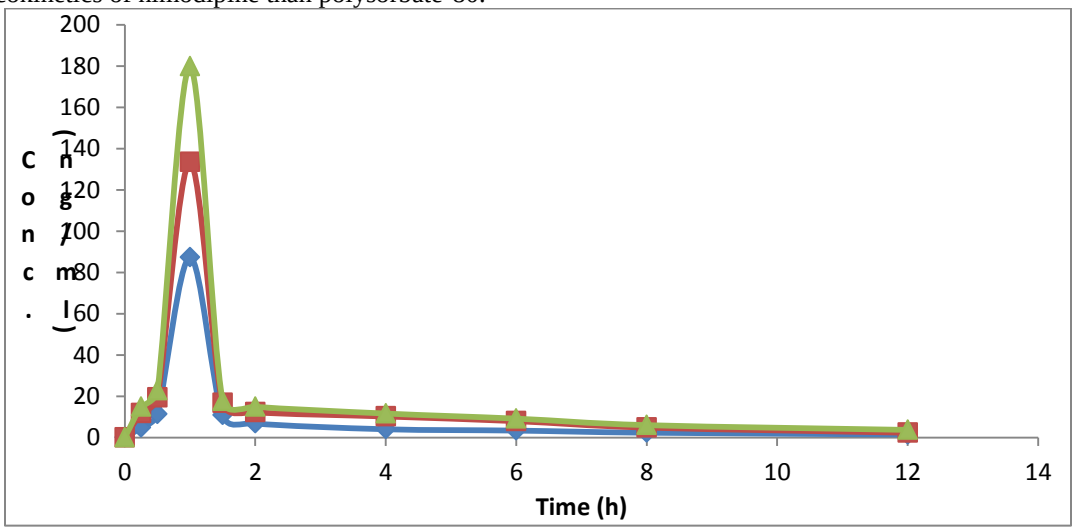

Figure 3: Plasma-concentration curve of nimodipine
□--------□ Control
□------□ Polysorbate-80 (Tween 80)
Δ------Δ Sodium lauryl sulfate

These vehicles were chosen because they are very often employed in the formulation of liquid or solid dosage forms of pharmaceutical active agents. Furthermore, the concentration of cosolvent or surfactant utilized in the present study has been clinically employed in the formulation of various pharmaceutical dosage forms.

A non-compartmental pharmacokinetic analysis was utilized to analyze the pharmacokinetic parameters of nimodipine. The maximum plasma concentration of nimodipine (Cmax) and the time to reach Cmax (Tmax) 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 clear¬ance (CLtotal) was estimated as dose (15mg/kg)/AUC0®∞ while volume of distribution at a steady state (Vss) as CLtotal × MRT. Division of 0.693 by the elimination-rate constant Ke (CLtotal/Vss) gave the elimination half-life (t½)

When compared with the control group, cosolvents and surfactants significantly ($p<0.05$) increased the (Cmax) and (AUCAUC®∞) of nimodipine. The increase in peak plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC®∞) by the studied vehicles showed that cosolvency and micellization could

enhance nimodipine bioavailability. The relative bioavailability (RB) of nimodipine when compared with the control are 1.6, 2.4, 2.0 and 3.4-fold increase for glycerol-water mixture, propylene glycol-water mixture, polysorbate-80-water mixture and sodium lauryl sulfate-water mixture respectively. Since nimodipine has excellent gastrointestinal tract absorption and very low systemic bioavailability due to extensive first-pass hepatic metabolism, the increase in the oral bioavailability by the studied vehicles, could be attributed to reduction in first-pass metabolism of nimodipine involving the inhibition of the cytochrome P450 (CYP3A subfamily) in the liver and reduction of the total body clearance. The findings agreed with previous studies [9, 10, 11] reporting cosolvents (including propylene glycol) and surfactants (including polysorbate 80) to be enhancers of pharmacokinetic features of drugs by inhibiting cytochrome P450 or P-glycoprotein efflux transporter. P-glycoprotein efflux transporter inhibition is considered not to be involved because nimodipine is not a substrate for this transporter.

CONCLUSION

Cosolveny and micellization significantly enhanced the oral bioavailability of nimodipine probably by cytochrome P450 inhibition. The investigation suggests that significant enhancement of bioavailability of nimodipine could be achieved in formulations containing propylene glycol and/or sodium lauryl sulfate respectively.

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