International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685, Impact Factor: RJIF 5.28
www.pharmacyresearchjournal.com
Volume 1; Issue 3; March 2016; Page No. 33-37

A Review on: Nicardipine Hydrochloride

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Abstract

Nicardipine hydrochloride, 2-(N-benzyl-N-methyl amino) ethyl methyl 1, 4-dihydro- 2, 6-dimethyl-4-(m-nitro phenyl)-3, 5-pyridinedicarboxylate mono hydrochloride, is a calcium antagonist with highly potent vasodilating activity and has been widely used for the treatment of hypertension and cardiovascular disease. Nicardipine hydrochloride is the hydrochloride salt preparation of Nicardipine and a potent L-type calcium channel protein inhibitor. Nicardipine is described to alter cytochrome P-450 3A expression through induction of CYP3A. Nicardipine blockade of Ca^{2+} channels has been correlated to antihypertensive effects. It belongs to a class II drug in BCS classification i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids which results into poor bioavailability after oral administration to improve the aqueous solubility and dissolution rate of the Nicardipine solid dispersions of drug using different methods were prepared and investigated. Enhancement of solubility of Nicardipine was observed with solid dispersion of drug using carriers such as [(NC: HPβCD): GMS: PEG4000] by fusion method. The observed results showed the solid dispersion of drug greater than the pure drug.

Keywords: Nicardipine, antagonist, vasodilating, BCS

Introduction

Gestational hypertension affects almost 10% of all pregnancies and worldwide approximately 50,000 women die from gestational hypertensive disorders each year. There is general agreement that maternal risks are decreased by antihypertensive treatment. So far, there is no consensus on the first choice antihypertensive medication. The most commonly used drugs for acute treatment of severe hypertension in pregnancy are: (di) hydralazine, labetalol and ketanserin. For many years (di) hydralazine has been used as a first choice therapy to treat severe hypertension in pregnancy. Side effects such as headache, nausea, and vomiting are common (up to 50%) and mimic symptoms of deteriorating preeclampsia. Results of a meta-analysis do not support the use of (di) hydralazine (compared to other antihypertensives) as first line treatment because of more maternal and fetal side effects with no evidence of a better antihypertensive effect.

Calcium antagonists have often successfully been prescribed during pregnancy, both for tocolysis and to treat hypertension during pregnancy. In these studies no severe maternal, fetal, or neonatal side-effects were observed. Pulmonary edema was observed (14) using nifedipine for tocolysis but this was in patients with a compromised cardiovascular condition (e.g., twin pregnancy, cho-rioamnionitis, cardiac disease).

Due to an increased risk of cardiac side-effects, headaches, and hot flushes, use of the fast acting calcium channel blocker nifedipine is not favored. Another calcium channel blocker, nicardipine, has a smaller negative inotropic effect and evokes fewer reflex tachycardia because of its more selective effect on blood vessels than nifedipine.

Nicardipine is licensed for use in acute severe hypertension and for postoperative hypertension. For these indications it shows a potent and fast reduction of the blood pressure after intravenous administration. Nicardipine seems to be very promising and may be a better alternative for the treatment of hypertensive disorders in pregnancy.

Calcium antagonists block the influx of calcium ions through voltage-operated calcium channels located in the cell membrane. Among the different groups, dihydropyridines is the most numerous and includes the largest number of novel compound. They act upon the L-type channel, which has a specific dihydropyridine site in its extra cellular surface and bind more selectively to vascular calcium channels than to those in the myocardium. Newer dihydropyridines exhibit greater selectivity, with evidence for a specific vascular vessel bed binding. Each of these agents is effective in the treatment of hypertension and angina pectoris.

An increased concentration of cytosolic Ca^{2+} causes increased contraction in cardiac and vascular smooth muscle cells. The entry of extracellular Ca^{2+} is more important in initiating the contraction of cardiac myocytes (Ca^{2+}-induced Ca^{2+} release). The release of Ca^{2+} from intracellular storage sites also contributes to contraction of vascular smooth muscle, particularly in some vascular beds. Cytosolic Ca^{2+} concentrations may be increased by various contractile stimuli. Thus many hormones and neurohormones increase Ca^{2+} influx through so-called receptor-operated channels, whereas high external concentrations of K^{+} and depolarizing electrical stimuli increase Ca^{2+} influx through voltage-sensitive, or "potential operated," channels. The Ca^{2+} channel antagonists produce their effects by binding to the a_1 subunit of the L-type Ca^{2+} channels and reducing Ca^{2+} flux through the channel.

Voltage-sensitive channels contain domains of homologous sequence that are arranged in tandem within a single large subunit. In addition to the major channel-forming subunit (termed a_1), Ca^{2+} channels contain several other associated subunits (termed a_2, b, g, and d). Voltage-sensitive Ca^{2+} channels have been divided into at least three subtypes based on their conductances and sensitivities to voltage. The channels best characterized to date are the L, N, and T subtypes; P/Q and R channels also have been identified. Only the L-type channel is sensitive to the dihydropyridine Ca^{2+} channel blockers. Large divalent cations such as Cd^{2+} and Mn^{2+} block a wider

range of Ca^{2+} channels. All approved Ca^{2+} channel blockers bind to the a_1 subunit of the L-type Ca^{2+} channel, which is the main pore-forming unit of the channel. This 200,000- to 250,000-dalton subunit is associated with a disulfide-linked a_2d subunit of approximately 140,000 daltons and an intracellular b subunit of 55,000 to 72,000 daltons. The a_1 subunits share a common topology of four homologous domains (I, II, III, and IV), each of which is composed of six putative transmembrane segments (S1-S6). The a_2d and b subunits modulate the a_1 subunit. The phenylalkylamine Ca^{2+} channel blockers bind to transmembrane segment 6 of domain IV (IVS6), the benzothiazepine Ca^{2+} channel blockers bind to the cytoplasmic bridge between domain III (IIIS) and domain IV (IVS), and the dihydropyridine Ca^{2+} channel blockers bind to transmembrane segment of both domain III (IIIS6) and domain IV (IVS6) [1-2]. Nicardipine has antianginal properties similar to those of nifedipine and may have selectivity for coronary vessels.

Chemistry of Nicardipine hydrochloride

Nicardipine hydrochloride is an organic salt derived from a 1, 4- dihydropyridine the chemical nomenclature whereof, according to the IUPAC (International Union of Pure and Applied Chemistry), is: (±)-2-(Benzylmethylamino) ethyl methyl, 4-dihydro-2, 6-dimethyl-4-(m-nitrophenyl) pyridine-3, 5-dicarboxylate hydrochloride and has the following structure: It is a greenish-yellow, odorless, crystalline powder that melts at about 169°C. It is freely soluble in chloroform, methanol, and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in n-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone, and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether, and hexane. It has a molecular weight of 515.99.

Molecular Weight: 515.98 g/mol.
Molecular Formula: $C_{26}H_{29}N_3O_6$•HCl

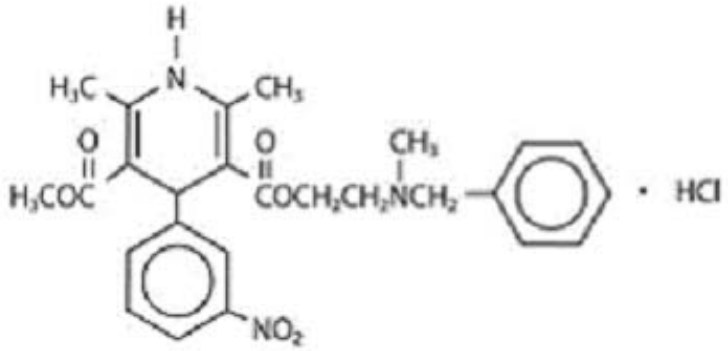

Fig 1: Nicardipine hydrochloride.

Predicted Properties of Nicardipine [3-5]

- Molecular Weight: 515.9859 g/mol
- Molecular Formula: $C_{26}H_{29}N_3O_6$•HCl
- Hydrogen Bond Donor Count: 2
- Hydrogen Bond Acceptor Count: 8
- Rotatable Bond Count: 10
- Exact Mass: 515.182313 g/mol
- Monoisotopic Mass: 515.182313 g/mol
- Topological Polar Surface Area: 114 A^2
- Heavy Atom Count: 36
- Formal Charge: 0
- Complexity: 856
- Isotope Atom Count: 0
- Defined Atom Stereocenter Count: 0
- Undefined Atom Stereocenter Count: 1
- Defined Bond Stereocenter Count: 0
- Undefined Bond Stereocenter Count: 0
- Covalently-Bonded Unit Count: 2

Mechanism of Action of Nicardipine hydrochloride

By deforming the channel, inhibiting ion-control gating mech anisms, &/or interfering with the release of calcium from the sarcoplasmic reticulum, Nicardipine inhibit the influx of extracellular calcium across the mayocardial and vascular smooth muscle cell membrane. The decrease in intracellular calcium inhibits thcontractile processes of the myocardial sm ooth muscle cells, causing dilation of the coronary and system ic arteries, increased oxygen delivery to the mayocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure Nicardipine is a dihydropyridine derivate with a strong inhibitor action on L-type Ca^{2+} channels resulting in inhibition of Ca^{2+} influx in cardiac and vascular smooth muscle cells. Nicardipine is a potent vasodilator and is 10,000 times more selective for vascular smooth muscle than cardiac muscle. Administration of nicardipine significantly decreases systemic vascular resistance (afterload). Cardiac out-put and ejection fraction increased following admin-istration of 40-mg nicardipine in hypertensive patients. Following an IV bolus the clinically important half-life is in the order of 2 to 5 minutes. How-ever, following a long-term IV infusion (24–48hours) the clinically important half-life is in the order of 1 to 2 hours. Compared to other antihypertensive agents used in pregnancy nicardipine has the shortest half-life. The effects on blood pressure are significantly correlated with nicardipine plasma con-centration.

In human studies, intravenous infusion of nicardipine achieved lower mean plasma levels in both the maternal and fetal circulations (54.6 and 4.18 ng/mL, respectively), but the 9% transplacental transfer of nicardipine is of the same order of mag-nitude. The current recommended dosage for rapid blood pressure control in non-pregnant patients is 5 mg/h, increasing the infusion rate by 2.5 mg/h every 5 minutes to a maximum of 15 mg/h. A dosage schedule during pregnancy has been suggested by Hanff et al (21): a starting dosage of 3 mg/h,

which is increased by 0.5 to 1 mg/h to a maximum of 10 mg/h until the target blood pressure is reached.

Pharmacokinetic of Nicardipine hydrochloride

Absorption

The onset of action of intravenous nicardipine is between 5 and 15 min with a duration of action of 4–6 hours. Once administered intravenously, nicardipine crosses the blood–brain barrier and reaches the nervous tissue, where it binds to calcium-channels of the L-type, acting primarily at the level of the hippocampus. Intravenous nicardipine has been shown to reduce both cardiac and cerebral ischemia.

Nicardipine is approximately 100% absorbed following oral a dministration. Cmax is 36-133ng/ml (Immediate release) & 13.4-58.4nm/ml (ER); Steady state is 24-48hr (IV); Tmax 0.5 to 2 hr (immediate release) and 1 to 4 h (ER); Absolute bioavailability is 35%. When administered 1-3hr after a high fat meal, Cmax & AUC were lower (20-30%for immediate release).

Distribution

Following infusion, plasma concentrations decline triexponeti ally with a rapid early distribution phase, intermediate phase, and a slow terminal phase. V_d is 8.3 L/kg; Protein binding is a pproximately 95%.

Metabolism

Metabolized extensively by the liver.

Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range. The pharmacokinetics of intravenously ad-ministered nicardipine is linear over the dosage range of 0.5 to 20.0 mg/h. Transplacental passage of nicardipine seems to be low. Plasma concentrations of nicardipine in the fetal monkey (7–35 ng/mL) reached only 6% of the maternal values (175–865 ng/mL).

Elimination

Eliminated by urine (less than 1% unchanged, 49% (IV) and 6 0% (oral) of dose recovered) and feces (43% (IV) and 35% (oral). Plasma Cl is 0.4 L/h/kg; Plasma half-life is 8.6 h (oral), Half-life is 2-4hr (oral), alpha Half-life is 2.7min (IV), beta Half-life is 44.8min (IV, gamma half-life is 14.4hr (IV).

Onset

Approximately 20 min (oral).

Tolerability

Efficacy and safety of nicardipine were assessed in 29,104 hypertensive nonpregnant patients. Most adverse reactions were transient and were related to vasodilatation: peripheral edema 7%, flushing 7%, and headache 4%. In a double-blind randomized study to evaluate the efficacy and safety of intravenous nicardipine for treatment of postopera-tive hypertension the following adverse effects were seen: hypotension (4.5%), tachycardia (2.7%), nau-sea/vomiting (2%), and headache (2%). In the pla-cebo group the incidence of adverse events was 2%. One case report described sinus bradycardia when intravenous nicardipine was used. The author, however, described 3 other possible causes for the event in this patient. Pulmonary edema was de-scribed using intravenous nicardipine for tocolysis. Contraindications to the use of nicardi-pine are hypersensibility to nicardipine, severe aortic stenosis, hypotension, and shock.

Review of literature on Nicardipine Hydrochloride

K Kavitha *et al.* developed and evaluated matrix-type transdermal therapeutic system containing Nicardipine hydrochloride with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results suggested no physicochemical incompatibility between the drug and the polymers. Three transdermal patch formulations (F1, F2, F3) consists of Hydroxypropyl methylcellulose E5 and Ethyl cellulose in the ratios of 2:0, 0:2, and 1:1, respectively were prepared. All formulations carried dimethyl sulfoxide as penetration enhancer and dibutyl phthalate as plasticizer in acetone and methanol (4:3) as solvent system. The prepared transdermal patches were evaluated for in vitro release, moisture absorption, moisture loss and mechanical properties. The diffusion studies were performed by using modified Franz diffusion cells. The formulation, F1 (Hydroxypropyl methylcellulose E5 alone) showed maximum release of 97.1887±0.568 % in 7 hrs, whereas F2 (Ethyl cellulose alone) showed maximum release of 66.9393±1.8120 % in 24 hrs. The formulation, F2 with combination of polymers (1:1) showed maximum release of 91.2275 ± 0.175 % in 24 hrs, emerging to be ideal formulations for Nicardipine hydrochloride. The developed transdermal patches increase the efficacy of Nicardipine hydrochloride for the therapy of hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina [6].

Bratu *et al.* Prepared Infrared spectra of inclusion compounds of triacetyl-β -cyclodextrin with nicardipine hydrochloride were compared and analysed with those corresponding to their physical mixture and the pure compounds, respectively. Different O–H stretch-ing vibrations, assigned to water molecules, were located in the Fourier Transform Infrared (FT IR) spectra of triacetyl- β -cyclodextrin, and its inclusion complex with nicardipine obtained by spray-drying (SD) method. Water molecules involved in various hydrogen bonds environments change their status during complexation process. Evidences are observed of the formation of the complex especially in the spectral regions of the amino and carbonyl stretching vibrations [7].

Satyabrata Bhanja *et al.* Microcapsules of Nicardipine Hydrochloride with a coat consisting of Cyclohexane and a polymer such as Ethyl cellulose by Coacervation phase separation induced by the addition of non-solvent. By Scanning Electron Microscopy, the microcapsules were found to be spherical, without aggregation, discrete and free flowing. The maximum percentage of drug content was found to be 82.12 % in formulation F1 with the drug: polymer ratio (4:1). Entrapment efficiency were found to be in the range of 80 % to 107%. The average particle size were found to be in the range of 123 µm to 88 µm. Percent of loose drug on surface were found to be in the range of 3.54% to 8.65%. All the formulations showed good flowability. The in-vitro drug release for all the formulations F1 to F9 were found to be 6.8% to 17.14% drug release in first hour and 56.87% to 98.8% drug release at the end of 12 hrs. Among the nine formulations, F4 shows maximum drug release i.e. 98.8% at the end of 12hrs.

All the formulations F1 to F9 were found to be Zero order drug release with Non Fickian diffusion mechanism. The FTIR study indicates that there was no drug interaction and complexation occur during the manufacturing process [8].

Hind Al-Zein *et al.* Prepared extended release waxy matrix tablet containing nicardipine–hydroxyl propyl β cyclodextrin complex. Firstly the most suitable binary system NC-HPβCD was selected in order to improve drug solubility in the intestinal media and then embedding the complexed drug into a plastic matrix, by fusion method, consists of glycerol monostearate (GMS) as an inert waxy substance and polyethylene glycol 4000 (PEG4000) as a channeling agent, after that the final solid dispersion [(NC:HPβCD):GMS:PEG4000] which was prepared at different ratios was mixed with other excipients, avicel PH101, lactose, and talc, to get a tablet owning dissolution profile complying with the FDA and USP requirements for the extended release solid dosage forms [9].

Kunal N. Patel *et al.* Prepared Push Pull Osmotic Pump (PPOP) tablets of Nicardipine Hydrochloride (NH). A 3^2 full factorial design was employed to optimize the amount of osmotic agent (X_1) and osmopolymer (X_2) as independent variables that influence the drug release. PPOP tablets of NH were prepared by direct compression method and evaluated for % Cumulative Drug Release (% CDR) at 540min. as dependent variable. Fabricated PPOP tablets were evaluated for weight variation, thickness, diameter, hardness, friability, drug content and in vitro release studies. Amount of osmotic agent and os mopolymer had a pronounced effect on % CDR due to its osmotic property. The transformed values of the independent and dependent variables were subjected to multiple linear regression analysis to establish a full-model second-order polynomial equation. The co mputer optimization process, contour plots and response surface plots predicted at the concentration of independent variables X_1, and X_2 (60mg, and 75mg respectively), for maximized response. The drug release from developed formulation was found independent of pH and agitational intensity. The in vitro release kinetics studies reveal that optimized batc h fits well with Korsmeyer Peppas model followed by zero order, Hixson Crowell, first order and then Higuchi's model. Korsmeyer Peppas model analysis indicated that the mechanism of drug release is non-Fickian transport. The stability profiles indicate that the physico-chemical properties of the tablets are not affected on storage at 40 ± 2ºC & 75 ± 5% RH up to 6 months [10].

F. S. Ghazy *et al.* Prepared Inclusion complexes of nicardipine HCl (NIC) with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) were prepared using different methods: co-evaporation, kneading and co-precipitation. Inclusion complexation in aqueous solution and in solid state was studied by the solubility method, Fourier transform-infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD). The solubility of (NIC) increased as a function of cyclodextrin concentration, showing Bs and AL type diagrams for (β-CD) and (HP-β-CD), respectively. The dissolution rate of (NIC) / cyclodextrin complexes were investigated and compared with those of the physical mixtures and pure drug. The dissolution efficiency of (NIC) increased by complexation with cyclodextrins to2.8-2.9 fold than (NIC) alone. Oral bioavailability in rabbits increased to~6 fold by complexation with (β-CD) [11].

T. Nagendra Babu *et al.* Prepared Nicardipine hydrochloride sustained release pellets which correlates the standards of marketed product by using HPMC and Ethyl Cellulose as polymers. And compare the in-vitro dissolution profiles of formulated pellets with various concentrations of HPMC and Ethyl cellulose. The in vitro drug release studies were carried out in pH 6.8 using dissolution test apparatus II. The pellets were placed inside the 900 ml dissolution medium and speed and paddle was set at 75 rpm. Samples (5 ml) withdrawn at a time interval of 0, 0.50, 1, 2, 6, 12 hours and same value of fresh medium were replaced. The samples were analysed for drug content pH 6.8 as blank at λ max 237 nm. The percentage drug release was plotted against time Compatibility study of drug and polymers were conducted by employing FTIR Spectral studies. In this FTIR studies along with drug, HPMC E5 and ethyl cellulose 7cps used. The order of drug release for optimised formulation followed first order. And the mechanism of drug release is non-fickian diffusion governed by Higuchi. In the drug loading stage total five formulations (F1, F2, F3, F4, and F5) are formulated and in these F4 chosen as optimized formulation because of its % yield and assay were within the limits [12].

N. M. Moursy *et al.* Prepared sustained release floating capsules. A hydrocolloid of high viscosity grade was used for the floating systems. The inclusion of sodium bicarbonate to allow evolution of CO_2 to aid buoyancy was studied. Polymers that retard drug release were included as copreci-pitates with the drug and/or as additives in the formulated capsules. Both simple powder mixing of the ingredients and granule preparation via wet granulation were used. Seven capsule formulae were pre-pared. The prepared capsules were evaluated in vitro by testing drug dissolution, floating time and the kinetics of drug release. In vitro evaluation of a commercially available conventional 20 mg capsule of nicardipine hydrochloride, "Micard", was carried out for comparison. The hydrocolloid used succeeded in effecting capsule buoyancy. Floating time increased with increasing the proportion of the hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. All of the seven floating capsule formulae prepared proved efficient in controlling drug release. The sustained release floating capsule formula-tion of choice was evaluated in vivo in comparison to "Micard" capsules using rabbits. Reversed phase HPLC with UV detection was used for drug determination in rabbit plasma. Plasma concentration time curves revealed a longer drug duration for administration in the sustained release formula than the conventional "Micard" capsule being 16 h in the former versus 8 h for the latter [13].

Harekrishna Roy *et al.* Prepared oral sustained release matrix tablet of complexed Nicardipine Hydrochloride by employing hydrophilic and hydrophobic polymers. Due to poor water solubility of the drug its bioavailability is dissolution rate limited. The purpose of the study was to increase the solubility of Nicardipine hydrochloride by cyclodextrin inclusion complex technique. Complexes of different molar ratio were prepared. Kneading method was employed for preparati on of inclusion complexes. Among different complexes, a co mplex with 1:1 molar ratio of drug and β-CD showed the highest dissolution rate. Matrix table ts were prepared by direct compression technique using differ ent concentration of polymers and selected complex. The blended powders and tablets were evaluated for various

physicochemical parameters as per official protocol. The *In-vitro* dissolution was carried out in acidic medium (pH 1.2) for 2hrs, followed by phosphate buffer dissolution medium (pH6.8) for next 12 hrs. The blended powders showed satisfactory flow properties andcompressibility. All the tablet formulations showed acceptable pharmacotechnical properties and complied with official speci fications. The *In-vitro* release pattern indicated that formulati on F7 was good releasing the drug for period of 12 hrs and was best fitted to higuchi release profile. The present study has demonstrated that the combination of hydrophobic and hydrophilic polymers effectively sustained the drug release for prolonged period of time and a minimum of 28% sodium alginate is required to retard the release of Nicardipine from matrix tablet for the period of 12 hours [14].

Summary

Nicardipine, a dihydropyridine calcium-channel blocker, is used alone or with an angiotensin converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina.

Calcium antagonists Nicardipine (nifedipine) have proven to be effective for treatment of severe hypertension in pregnancy. Nicardipine seems to be preferable when compared to nifedipine because of its smaller negative inotropic effect, fewer reflex tachycardia, and less persistent severe hypertension. Based on the present study, nicardipine is a very effective therapy for treatment of severe hypertension and may be a better alternative than the other available treatment options.

It is 100 times more water soluble than is nifedipine, and therefore it can be administered intravenously, making nicardipine an easily titratable intravenous calcium channel blocker.

In common with other dihydropyridine, Nicardipine offers placebo-like Safety and tolerability in hypertensive patients. Nicardipine's pharmacological profile, including a long elimination half-life, results in an excellent trough: peak ratio and sustained control of blood pressure throughout the once-daily dosing interval.

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