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Research Article

Nicardipine: Concise Review on Analytical Techniques

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Abstract

Nicardipine (NCD) is the dihydropyridine class of calcium channel blockers. This study exits a concise review of analytical methods for the quantification of NCD in pharmaceutical preparations and biological fluids. NCD accessible single or in combination with added drugs in pharmaceutical matrices with many drugs like nifedipine, isradipine, veramipril, amlodipine and Aliskiren. They include numerous analytical techniques defined in this study for NCD were high-performance liquid chromatography (HPLC), UV-spectrophotometry, spectrofluorometry, electrochemical methods and liquid chromatography-mass spectroscopy (LCMS). The concise review explains the percentage utilization of the various approaches for analysis of NCD.

Keywords: Nicardipine; Review; Analytical method; Chromatography

Abbreviations: NCD: Nicardipine; NCD HCl: Nicardipine hydrochloride; AML: Amlodipine; NIF: Nifedipine; ISRA: Isradipine; VRP HCl: Verapamil hydrochloride; DTZ HCl: Diltiazem hydrochloride; FLN: Flunarizine; ALI: Aliskiren; MP: Metoprolol; TRB: Terbutaline; PRO: Propranolol; OXA- Oxazepam; FLUX: Fluoxetine; PIND: Pindolol; SDS: Sodium dodecyl sulphate; TEA: Triethylamine; LCMS: Liquid chromatography- mass spectroscopy; LC/MS/MS: Liquid chromatography- mass spectroscopy- mass spectroscopy; LC-ESI-MS: Liquid chromatography-electrospray- mass spectrometry; RSD: Relative standard deviations; ACC: Accuracy; PRECI: Precision; SS: System suitability; RF: Retention factor; RT: Retention time; TP: Theoretical plate; TF: Tailing factor; RES: Resolution; FR: Flow rate; nm: Nanometre; PDA: Photodiode array detector; SDM: Second derivative method; CAN: Acetonitrile; FA: Formic acid; GCE: Glassy carbon electrode; MPE: Mercury pool electrode; PE: Platinum electrode; CPE: Carbon paste electrode; PMDE: Paste mercury drop electrode; HMDE: Hanging mercury drop electrode

Introduction

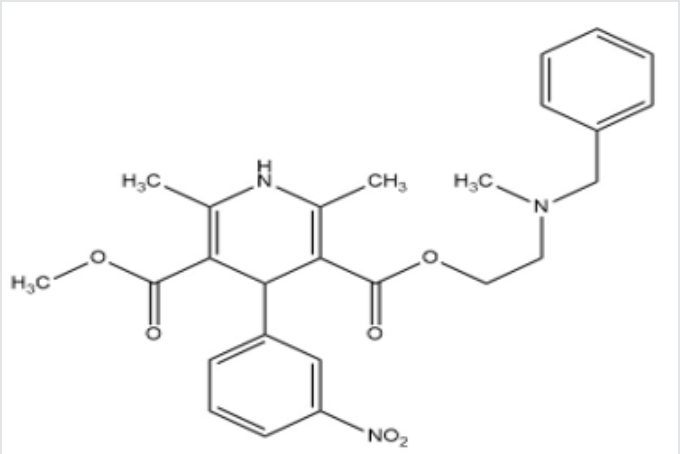

Figure 1: Structure of Nicardipine.

Nicardipine is chemically identified as 1, 4-Dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-3, 5-pyridinedicarboxylic acid methyl 2-[methyl-(phenylmethyl) amino]ethyl ester (Figure 1). The molecular weight of NCD is 479.52 [1]. The melting point of NCD in the range of 136-138 °C (277-280 °F) [2].It is a calcium channel antagonist class of dihydropyridine. It is now used for the treatment of angina pectoris and similarly used in the managing of hypertension [3]. Most CCBs, including amlodipine, felodipine, isradipine, nicardipine, and nifedipine, belong to the dihydropyridine class [4]. The dihydropyridine have little direct effect on cardiac tissue at typical therapeutic levels; yet, they can evoke reflex tachycardia [5].

The schematic diagram shows the molecular mechanism of NCD (Figure 2). The CCBs indicated a number of important differences from the pharmacokinetic and pharmacodynamics point of views as well as for selectivity and duration of pharmacological action, while distribution the equal ability to interact with L-type voltage-dependent transmembrane calcium channels [6,7].

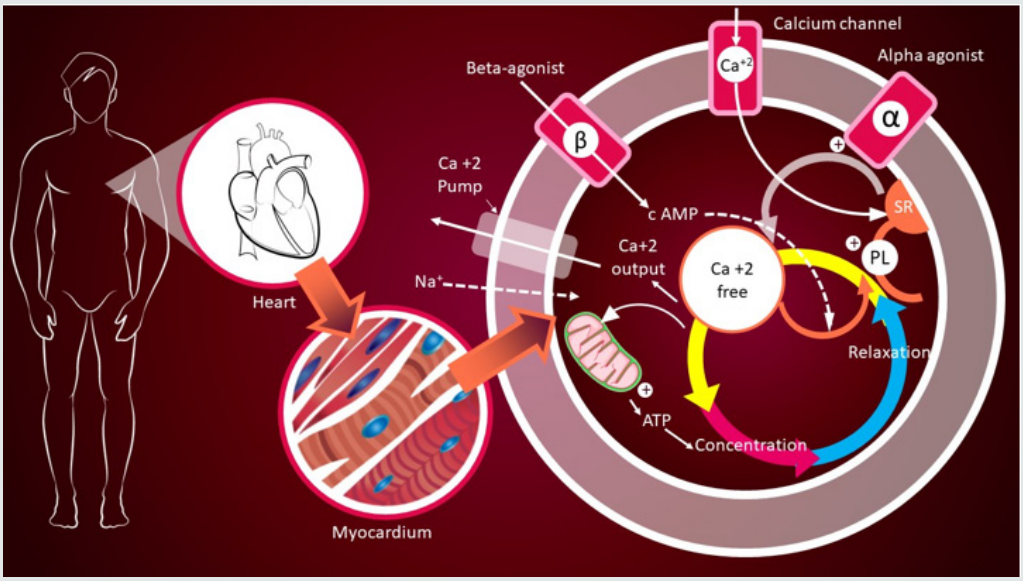

Figure 2: Schematic representation to explain the molecular mechanisms of actions of calcium channel blockers (CCBs).

Chemistry of NCD

It is a synthetic derivative of potent calcium channel blocker and nitrophenyl-pyridine [8]. The IUPAC name of nicardipine is 5-O-[2-[benzyl (methyl) amino] ethyl] 3-O-methyl 2, 6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [9]. The molecular formula is $C_{26}H_{29}N_3O_6$ and molecular weight is 479.533 g/mol [10]. NCD clinical properties and molecular mechanisms closely similar to those of nifedipine and the other dihydropyridine but nicardipine is extra selective for coronary and cerebral blood vessels. As compare to nifedipine the nicardipine have longer half-life [11].

Pharmacokinetic Properties

Almost 95% of nicardipine is bound by serum proteins, precisely α1-acid glycoproteins (AAG), albumin, and lipoproteins [4]. Nicardipine plasma elimination half-life has reached between 44 to 107 minutes in maximum studies with clearance of the drug due mostly to hepatic mechanisms [12]. The orally directed nicardipine is speedily absorbed and peak plasma concentrations arising between 20 minutes and 2 hours [13]. Distribution volume in normal volunteers have reached between 0.6L/kg to 63L. Lower than 0.03% of parent drug is enhanced from the urine of humans [14].

Pharmacodynamics Properties

Oral doses and intravenous of nicardipine may create rises in heart rate of up to 30% and 8 to 26% and dose-related reductions in mean arterial blood pressure correspondingly, and the duration of these effects which may be as long as 3 hours have generally been greater in patients at rest than in those at exercise [15,16]. While decreases in blood pressure have been efficiently preserved for some months without indication of tachyphylaxis, increases in heart rate occasionally seen after acute administration are not detected later extensive time oral treatment [15].

Nicardipine is related to further peripheral vasodilators (Figure 3) [17]. Nicardipine constrains the influx of extra cellular calcium crosswise the myocardial and vascular smooth muscle cell membranes maybe by deforming the channel [18]. The reduction in intracellular calcium constrains the contractile developments of the myocardial smooth muscle cells, affecting dilation of the coronary and systemic arteries, enhanced oxygen transfer to the myocardial tissue, diminished total peripheral resistance, reduced systemic blood pressure, and decreased afterload [19].

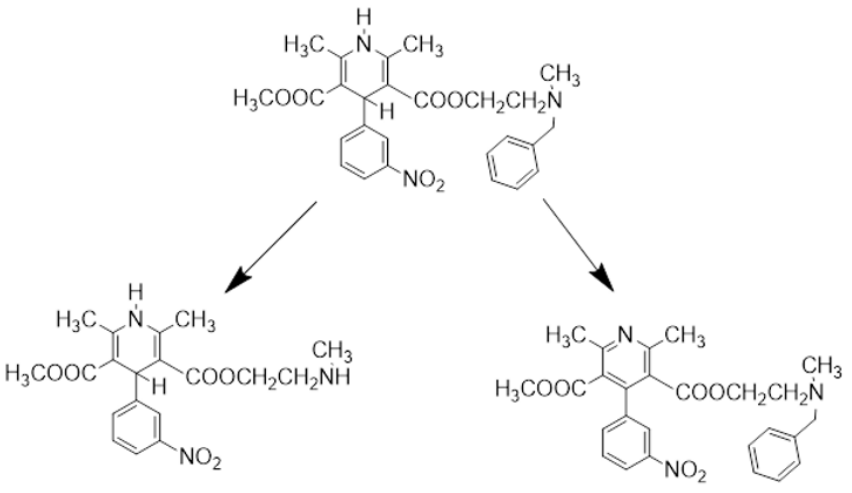

Figure 3: The proposed in vitro metabolic pathways of nicardipine in human liver microsomes are illustrated in, [4].

Analytical Method

The substantial literature survey exposed that, the development and validation of analytical methods for identification and quantification of drugs and other molecules of interest in Pharmaceutical Matrices [20,21]. Various analytical methods were developed viz HPLC, UV/Visible spectrophotometry, spectrofluorometric, LC-MS and voltammetry for estimation of NCD the dosage form [22]. The proposed method represents the determination of NCD in single and simultaneous method with Nifedipine, Isradipine, Aliskiren, Amlodipine, Verapamil HCl, Diltiazem HCl and Flunarizine [23].

Bioanalytical Method

Validated, Choosy and complex analytical systems for the quantifiable estimation of drugs and their metabolites (analytes) and biomarkers are serious for the effective manner of nonclinical and biopharmaceutics and clinical pharmacology studies [24,25]. Validating bioanalytical techniques contains carrying out all of the processes that establish that a specific method used for quantifiable measurement of analytes in a certain biological medium (e.g., blood, plasma, urine, or serum) is reproducible and dependable for the proposed use [26].

Analytical Acounts on Nicardipine

HPLC

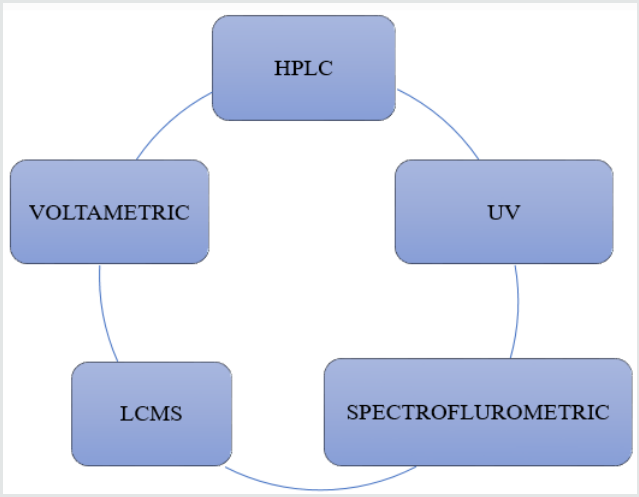

Figure 4

(Figure 4) The technique of high performance liquid chromatography (HPLC) was established in the late 1960s and early 1970s from knowledge of the theoretical principle that already had been recognized for the earlier chromatographic technique [27]. The method is created on the same modes of separation as classical column chromatographic, i.e. adsorption, partition (including reversed-phase partition), ion exchange and gel permeation, but it differs from column chromatography in that the mobile phase is

pumped over the packed column underneath high pressure [28,29]. Estimation of NCD single or in combination with added drugs in pharmaceutical matrices and biological fluid by HPLC are note down in (Table 1 & 2) [30].

Table 1: Dosage forms, route of administration and mention dose of nicardipine [6].

Dosage Form	Route of Administration	Indication/ Dose
Immediate release	oral	Hypertension
		Initial dose: 20 mg orally 3 times a day
		Maintenance dose: 20 to 40 mg orally 3 times a day
		Angina Pectoris Prophylaxis
		Initial dose: 20 mg orally 3 times a day
		Maintenance dose: 20 to 40 mg orally 3 times a day
		Congestive Heart Failure
		Initial dose: 20 mg orally 3 times a day
		Maintenance dose: 20 to 40 mg orally 3 times a day
Sustained release	oral	Hypertension
		Initial dose: 30 mg orally twice a day
		Maintenance dose: 30 to 60 mg orally twice a day
		Angina Pectoris Prophylaxis
		Initial dose: 30 mg orally twice a day
		Maintenance dose: 30 to 60 mg orally twice a day
		Congestive Heart Failure
		Initial dose: 30 mg orally twice a day
		Maintenance dose: 30 to 60 mg orally twice a day
IV infusion	oral	Hypertension
		20 mg orally every 8 hours is equivalent to 0.5 mg/hour via IV infusion
		30 mg orally every 8 hours is equivalent to 1.2 mg/hour via IV infusion
		40 mg orally every 8 hours is equivalent to 2.2 mg/hour via IV infusion
		Angina Pectoris Prophylaxis
		20 mg orally every 8 hours is equivalent to 0.5 mg/hr IV infusion
		30 mg orally every 8 hours is equivalent to 1.2 mg/hr IV infusion
		40 mg orally every 8 hours is equivalent to 2.2 mg/hr IV infusion
		Congestive Heart Failure
		20 mg orally every 8 hours is equivalent to 0.5 mg/hr IV infusion
		30 mg orally every 8 hours is equivalent to 1.2 mg/hr IV infusion
		40 mg orally every 8 hours is equivalent to 2.2 mg/hr IV infusion

Table 2: HPLC analytical determination of NCD.

Sr.No	Drugs	Matrix	Column	Mobile phase	Detector	Linearity	ACC & Preci	LOD & LOQ	System suitability	Ref
1	NCD HCL	Pure form	RP C-18 Column	Methanol & potassium dihydrogen phosphate (70:30 v/v)	UV-Vis spectro-photometer	10-60 µg/mL	Acc- 99.15% - 99.35% Preci-Interday -1.00% - 1.43% Intraday-1.09% - 1.44%	LOD-430 ng/mL LOQ-130 ng/mL	RT-3.71 TP - 3905.89 TF –1.489	(15)
2	NCD	Bulk	C18 column	Methanol: ACN (90:10)	UV-Vis detector	2.5-12 µg/mL	Acc- 100.91 - 98.15 Preci- Interday-40.87 Intraday- 45.08	LOD-0.803 0.803ug/ml µg/mL LOQ-2.411 µg/mL 2.411ugml	RT-3.34 TP-7660 TF -1.81	(16)
3	NCD HCL	Bulk and Tablet	C18 column	ACN -ammonium acetate (70:30, v/v)	Photo diode array detector	0.3 – 100 µg /mL	Acc- 99.5 – 100.6 %) Preci- RSD-1 %.	LOD -130 ng /mL LOQ- 393 ng /mL	RT-3.8 TP-3972	(17)
4	NCD HCL	Tablet	C18 (250 x 4.6)mm,5u column	Triethylaminephosphoric acid buffer (pH-3.5 by orthophosphoric acid, acetonitrile (35:65, v/v)	UV detector	10-50 µg /mL	Acc- 98.73 -102.11% Preci- % RSD 0.66	-	RT-9.867 TP-8600	(18)
5	NCD HCL	Pure form and capsules	BDS-C18 column	Sodium acetate/acetic acid buffer (pH 4.5) and acetonitrile (20:80, v/v)	UVB50 varian detector	5-40 µg /mL	Acc- % RSD-0.17	-	-	(19)
6	NCD and ALI	Tablet dosage forms	RPHPLC C-18 hypersil ODS	Phosphate buffer and ACN (40 : 60% v/v)	PDA detector	NCD-2 to 15 µg/mL, ALI-30 to 55 µg/mL	Acc- ALI & NCD 99.99 & 101.7%	NCD- LOD 0.1336 µg/mL LOQ 0.4049 µg/mL	-	(20)
7	NCD	Pure form	ACE C8 (250_4.6 mm, 5 mm) column	Buffer and ACN in (75:25 v/v), Milli-Q water and ACN in 25:75 v=v	PDA detector	-	Acc- 87.3 to 103.1% Preci- RSD (%)- 2.7	LOD-0.035 µg/mL LOQ-0.085 µg/mL	-	(21)
8	NCD HCL	Capsules	kromasil C18 column	ACN & 0.03 % v/v phosphoric acid (40:60v/v)	PDA Detector	0.5-µg/mL	Acc- 98-102% Preci- Interday-0.46% Intraday-0.65%	-	TP –4025.5 TF –1.5 RES- 6.385	(19)

9	NCD	Pure form	SB-CN Zorbax column	ACN /methanol/0.02M monobasic potassium phosphate 20:30:50 v/v	UV Detector	1–100 µg/mL	-	-	-	(20)
10	NCD	Pure form	C18 column	ACN e-0.01 M triethylamine (pH 3.0 with 0.75 M H3PO4) (40:60, v/v)	UV-visible detector.	0.02-2 µg/mL	Acc- 0.096 to 1.92 lag mL^{-1}. Preci- Interday-0.83 % Intraday- 6.0 %	LOD- 0.009 µg/ mL	-	(21)
11	NCD	Pure form	cartridge column packed with 5 µm LiChrospher 100 RP-8	Phosphate buffer - ACN - methanol (600 : 370 : 65)	PDA detector	30 to 150 µg/mL	Acc- 98.8% Preci- Interday- Intraday-0.89 %	LOQ- 0.2%	-	(22)
12	NCD HCL	Tablets & capsules	Hibar Lichrosorb CN (10 /.tm)	0.01 M sodium phosphate buffer at pH 6.1 and CH3CN (1:1).	UV-Vis detector	0.5 and 20 µg/mL	-	-	-	(23)

Analytical Determination of NCD

Tiwari R N et al. [31] initiated validation and Development of an analytical method for the RP- HPLC for nicardipine hydrochloride. Kromacil C-18 column on an isocratic mode was developed and separation was done by a mobile phase comprising methanol and potassium dihydrogen phosphate (70:30v/v) and pH of buffer scheme was used to 3.0 through ortho phosphoric acid. UV observation at 236nm and flow rate was retained 1ml/min. The LOD and LOQ were originate to be 430ng /mL and 130ng /mL. The linearity of the suggested method in the series of 10-60µg/ml, with a regression coefficient of 0.9994 and the % recovery was 99.15% to 99.35%.The established process can be used for the repetitive analysis and assay of nicardipine HCl in quality control laboratories.

Veena S. Kasture et al. [32] initiated a isocratic RP-HPLC method was developed and validated for Nicardipine hydrochloride in bulk and formulation.C18 column with dimension on 25 x 0.6cm and the mobile phase containing the of mixture of methanol: acetonitrile in proportion of (90:10). The UV observation was carried out at wavelength 354nm. The LOD and LOQ were originate to be 0.803µg/ml and 2.411µg/ml. The linearity of the suggested method in the series of 2-12µg/ml.

Jyoti Salvekar et al. [33] initiated stability indicating RP-HPLC method was established and formalize for nicardipine hydrochloride (NC) in the occurrence of its degradation products. The linearity of the suggested method in the series of 0.3-100µg/mL. C18 column with dimension 150mm length, 4.6mm ID and 5µm particle size was used for the method expansion and chromatographic separation was done by a mobile phase comprising a combination of aqueous 0.1M ammonium acetate and acetonitrile in the proportion (30:70, v/v). The flow rate and detection wavelength were 1.2mL min^{-1} and 237nm. The LOD and LOQ were originate to be 130ng/ mL and 393ng/ mL.

Milind B. Ubale et al. [34] Established stability-indicating isocratic reversed phase high-performance liquid chromatographic method was established and validated for quantifiable determination of Nicardipine hydrochloride in bulk drugs. Method was developed using C18 (250 x4.6)mm, 5um column and separation was achieved by using a mobile phase used of triethylaminephosphoric acid buffer (pH-3.5 by orthophosphoric acid, acetonitrile (35:65,v/v). The method was linear in the range of 0.3-100µgmL-1 nicardipine concentration [35]. The flow rate and detection wavelength were 1.0ml/min and 353nm.

Shahul Hameed M et al. [36] Established analytical RP-HPLC method for simultaneous estimation of Aliskiren Hemifumarate and Nicardipine Besylate from. Method was developed C-18 hypersil ODS column and separation was achieved by using a mobile phase containing phosphate buffer and acetonitrile (40 : 60% v/v). The method was linear in the range for Nicardipine 2 to 15µg/mL and Aliskiren 30 to 55µg/mL concentration. The flow rate and detection

wavelength kept at 1mL/min and at 237nm. The LOD and LOQ were found to be for Aliskiren Hemifumarate and Nicardipine Besylate 0.1614µg/mL and 0.1336µg/mL and 0.4890µg/mL and 0.4049µg/mL. . The percent recovery for Aliskiren and Nicardipine in ranged 99.99 and 101.7% and correlation coefficient (R^2) were 0.9990 [36].

Bioanalytical determination of NCD

Sheikha M. Al-Ghannam et al. [37] Initiated reversed-phase liquid chromatography method was established for the purpose of nicardipine hydrochloride in human plasma. Nicardipine were initially extracted from hexane-butanol (12:1v/v). Nicardipine was separated by HPLC C-18 column and quantified by ultraviolet detection at 353nm. A mixture of methanol/TEA buffer (0.01M) pH 4 with acetic acid (70:30v/v) was used as mobile phase. The linearity of the proposed method in the range of 15-200µg/ml, with a regression coefficient of 0.9991 and the % recovery was 99.15% to 99.35%. The LOD and LOQ were originate to be in plasma 11.74 and 35.57ng/mL. The RSD of intra- and inter-day examination for NCD in plasma were 2.7-3.7% and 1.9-3.6% [37].

P. Bhaskar et al. [38] Established high-performance liquid chromatographic method for the nicardipine hydrochloride in human plasma. RP C-18 was used for separation with mobile phase comprising acetonitrile: 0.02M potassium dihydrogen phosphate (pH 4.0) in the proportion of 60:40v/v. Ultraviolet detection was conceded at 239nm. Extracted with ethyl acetate. The method proved to be linear in the choice of 5-150ng/0.5 mL of plasma with a regression coefficient (r^2) of 0.9987. The run time was fixed at 10 minutes. The range of percentage of RSD for intra-day analyses inter-day analyses was smaller than 2.5% and limit of detection 2.5ng/0.5mL in plasma.

M. I. Walash et al. [39] Initiated a isocratic reversed phase stability-indicating HPLC technique was established and validated for quantifiable purpose of nicardipine hydrochloride. Nicardipine was separated by a Hibar-C18 (150 _ 4.6mm i.d.) stainless steel column. A mixture of was used as mobile phase 10% n-propanol, 0.175 M SDS, 0.3% TEA in 0.02 M phosphoric acid of pH 6.5. The method was linear for 1-40 and correlation coefficient (R2) were 0.9999.The flow rate were 1 ml/min. The LOD and LOQ were found to be 0.024µg/ml and 0.08µg/ml. The mean % recovery 100.12+0.28 and 100.87+0.41, respectively.

R.M. Alonso et al. [40] They performed high-performance liquid chromatographic technique using electrochemical detection for the estimation of six 1,4-dihydropyridines. Method was established by means of a Supelcosil LC ABZ1Plus C column and mobile phase comprising methanol-18 water (70:30), containing 2mM CH COOH-CH COONa. The intra-day difference was originate to be smaller than 5.0%. The flow rate were 1ml /min. The method was linear for 50-1000ng/mL and correlation coefficient (R^2) were 0.9998. The relative standard deviations of intra -day and inter-day analysis for NC 2.46-3.90 and 10.2-11.5% in plasma. The relative standard devation were create to be 4.6% .

Sheikha M. Al-Ghannam et al. [41] They performed stability indicating RP-HPLC technique for the purpose of nicardipine (NC) in the presence of its degradation products. They used C18 (150mm, 3.9mm, 5lm) analytical column with UV observation at 353nm. A mixture of 70% methanol: acetic acid comprising 0.01M triethylamine with pH 4 was handed-down as the mobile phase with flow rate of 1.0mL/min. The calibration curve is linear over the concentration range 0.5-40µg/mL with R^2 was originated to be 0.9991. The LOD and LOQ were found to be 0.011µg mL-1 and 0.036µg /mL, respectively. The mean % recoveries of 100.11± 2.26%, respectively.

Spectrophotometry Method

Inside the literature about 9 methods were designated for the assessment of NCD using spectrophotometry, of which 6 methods are for estimation NCD alone, while the others NCD in combination with other drug substances. In the literature also, 2 spectrofluorometric methods have been established of NCD in tablets [42,43]. Spectrophotometric and spectrofluorometric methods have been presented for the determination of NCD alone and in Combinations are note down in (Table 3) [44].

Estimation of NCD as single entity

Hayam Mahmoud Lotfy et al. [45] A confirmed humble and discriminating spectrophotometric method was established for simultaneous purpose of nicardipine in presence of its alkaline induced degradation products. The curve is linear in the choice of 2-18µg/mL. They dignified first derivative (D1) spectra and the second derivative (D2) at 382.3 and 239nm. The ratio derivative measured by the largeness at 244nm.

Amala Mateti et al. [46] They performed specific and correct technique has been developed and subsequently validated for estimation of Nicardipine hydrochloride. The linearity of the suggested method in the series of 5-25µg/ml, with R^2 created to be 0.999. Acetonitrile: water (50:50) solvent were used and absorbtion maxima were 235 nm. The process found to be exact and precised. The LOD and LOQ were originate to be 0.3130µg/ml and 0.1032µg/ml.

Estimation of NCD in Combinations

S. M. AL-Ghannam et al. [47] Developed simple spectrophotometric technique was established for the purpose of 1,4-dihydropyridine composites for simultaneous determination of NCD and ISRA either in unpolluted form. Absorption maximum for red product were at 546 and 539nm with NCD and ISRA, respectively. The method were linear in series of 8.0-180µg/ml with the LOD of 1.67µg/ml for NCD and 8.0-110µg/ml with the LOD of 1.748µg/ml for ISRA.

Table 3: HPLC bioanalytical methods for NCD.

Sr.No	Drug	Matrix	Column	Mobile Phase	Detector	Linearity	LOD & LOD	Ref	ACC & Preci
1	NCD	Pure form	C-18 column	Methanol–triethylamine buffer (0.01M) pH 4 with acetic acid (70:30)	PDA Detector	25-150 ng/mL	Acc-99.15% -99.35% Preci-Interday-2.7-3.7 % Intraday-1.9-3.6 %	LOD-11.47 ng/mL LOQ-35.57 ng/mL	(24)
2	NCD HCL	Pure form	C-18 column	ACN – 0.02 M sodium phosphate buffer–methanol (45:40:15) with 0.2% of triethylamine	UV detector	5–100 ng/mL	Accu-83.94 ± 3.87 % Prici-Interday-4.71–9.38% Intraday-3.26–6.52%	-	(25)
3	NCD HCl	capsules	RP C-18 column	ACN: 0.02M potassium dihydrogen phosphate (pH 4.0)	UV/VIS Detector	5 to 150 ng/mL	Acc-95.04± 3.09 Prici-Interday- 99.98 ± 1.56 Intraday- 100.10 ± 1.65	LOD-2.5 ng/mL	(26)
4	NCD HCl	Pure form and capsules	RP Hibar-C18 column	0.175 M sodium dodecyl sulphate, 10% n-propanol, 0.3% triethylamine in 0.02 M phosphoric acid of pH 6.5	UV Detector	1–40 µg/mL & 2–20 µg/mL	Accu-1.93-5.05 Preci-Interday-97.70-102.90 Intraday-103.20-120.60	LOD- 0.024 & 0.072 µg/mL LOQ-0.08 & 0.24 µg/mL	(27)
5	NCD + AML	Pure form	RP-18e column	Ethylenediamine with tetrahydrofuran (1:1, v/v) solutions	UV/VIS Detector	0.5–50.0 ng/mL	Acc-NCD-75.5% Prici-Interday-8.9-14.9 % Intraday-4.6-14.6 %	-	(28)

6	NCD	Tablets	C-18 Column	ACN – KH2PO4 buffer (0.015 M, pH = 5.5) – triethylamine	UV200 multiwavelength detector	5–200 ng/mL	Accu- 92.8–100.8% Prici- Interday- 5.2–6.4% Intraday- 3.5–5.4%	-	(29)
7	NCD	Pure form	C-18 Column	Methanol–water (70:30)	Electrochemical detector	50–1000 ng/mL	Accu- 76% Preci- Interday- 10.2 to 11.5% Intraday- 2.46 to 3.90%	-	(30)
8	NCD	Pure form	C-18 Column	n-hexane- 1,2-dichloroethane-methanol-trifluoroacetic acid (250:40:10:1, v/v)	UV-880 ultraviolet detector	5-100 ng/mL	Accu- 98.4-92.8	-	(31)
9	NCD	Capsules	C-18 Column	70% methanol: acetic acid containing 0.01 M triethylamine with pH 4	PDA Detector	0.5-40 µg/mL	Accu- 99.04 ± 5.67% Prici- Interday- 1.2%. Intraday- 1.2%.	LOD-0.011 µg/mL LOQ-0.036 µg/mL	(32)
10	NCD HCl	Pure form	C-18 Column	Ethanol and water (70:70)	UV/VIS Detector	0.001-2 µg/mL	-	-	(33)
11	NCD	Pure form	C-18 Column	ACN –0.02 M NaH PO4	UV Detector	5-100 ng/mL	Accu- Preci- Interday- 5.0% Intraday- 2.9 %	LOD-1.6 ng/mL LOQ- 5.4 ng/mL	(34)

Sayed M. Derayea et al. [48] They performed spectrophotometric technique was designated for purpose of AML and NCD in bulk precipitates and pharmaceutical preparation. The absorption maxima were at 549nm. The process linear in the series of 5-60µg/ml for both drugs i.e. AML and NCD and correlation coefficients for amlodipine and nicardipine were (0.9981 and 0.9995). The LOD and LOQ were found to be 1.8 and 1.2µg/ml and 6.0 and 3.6µg/ml for both drugs. The mean percentage recoveries were created to be 100.04 ± 0.83 and 99.98 ± 0.80.

Ahmed A. H. Abdellatif et al. [49] They was described spectrophotometric technique for purpose of NIF and NIC in their pharmaceutical preparations. The method originated in series of range 2.0 to 12.0µg/mL with quantitation limit 1.4 and 1.9µg/mL. The mean percentage recoveries were established to be 98.2±0.3 to 99.5±0.3% NIF and NIC, individuallyd.

Spectrofluorometric Methods

Sheikha M. Al-Ghannam et al. [50] They implanted spectrofluorometric process for estimation 1,4-dihydropyridine compounds in pharmaceutical preparations and organic fluids. The nicardipine, nifedipine and isradipine were rectilinear above the series of 0.4- 6.0, 0.2-4.0 and 0.1-9.0µgml^{-1} and detection limit found to be 0.0028, 0.017 and 0.016µgml-1, correspondingly.

M. I. Walash et al. [51] They implanted sensitive spectrofluorometric method for estimation calcium channel blockers namely, verapamil hydrochloride, diltiazem hydrochloride, nicardipine hydrochloride and flunarizine. The fluorescence intensity-concentration plots for all compounds were linear over the ranges of 0.01 to 0.12 µgmL^{-1}. The LOD for all compounds in ranged from 2.93 × 10^{-3} to 0.012µg mL^{-1} and LOQ from 9.76 × 10^{-3} to 0.04µg mL^{-1} were produced (Table 4).

Table 4: Spectrophotometric and Spectrofluorimetric methods for estimation of NCD alone and in combined dosage form.

Sr.No	Drug	Method	Matrix	Linearity	LOD/LOQ	Correlation coefficient (R2) Value	Ref
1	NCD	Second derivative method (SDM) 382.3 and 239 nm	Bulk	2-18 µg/mL	LOD- D1 method-0.21 D2 method-0.24 DD1 method-0.27 RD-0.14 LOQ- D1 method-0.62 D2 method-0.74 DD1 method-0.84 RD-0.43	D1-0.99 D2-0.99 DD1-0.99 RD-0.99	(35)
2	NCD HCL	UV spectrophotometric method 235nm	Bulk and tablet dosage form.	5-25 µg/mL	LOD- 0.3130 µg/ml LOQ- 0.1032 µg/ml	0.999	(36)
3	NCD + ISRA	Spectrophotometric method 546 and 539 nm	Tablet and Capsules	NCD- 8.0–180 µg/mL ISRA- 8.0-110 µg/mL	LOD- NIC-1.67 µg/ml ISRA- 1.74 µg/ml LOQ- NIC – 5.58 ISRA-5.27	NCD- 0.9960 ISRA-0.9970	(37)
4	NCD	Spectrophotometric Method 500 nm	Tablets and capsules	5 - 70 µg/mL	LOD- 0.750 µg/mL LOQ- 2.500	NCD- 09994	(38)
5	AML + NCD	Spectrophotometric method 549 nm.	Pure form	NIC & AML- 5-60 µg/mL	LOD- AML-1.8 NIC-1.1 LOQ- AML-6.0 NIC-3.6	NCD-0.9995 AML-0.9991	(39)
6	NCD + NIF	Spectrophotometric method NIF-434 nm NIC-441 nm	Tablets and Capsules	2.0 to 12.0 µg/mL	LOD- 1.4 and 1.9 µg/mL	NCD-0.983 NIF-0.991	(40)
7	NCD	Spectrophotometric methods 380nm	Tablets	1.0-10.0 µg/mL & 2.0-10.0 µg/mL	-	Meyhod A- 0.9832 Method B- 0.04472	(41)
8	NCD	Spectrophotometric methods 254 nm.	Pure form	0.29 n 0.79 µg/mL	LOD- 8.18 µg/mL LOQ- 25.38 µg/mL	NCD- 0.9955	(42)

9	NCD	spectrophotometric method 332 nm and 356 nm	Pure form	1.0_10_5 M NF and 0.5_10_5 M NC	-	NIF- 0.9974 & NCD- 0.9951	(43)
10	NCD + NIF + ISRA	spectrofluorometric method NCD- 460/364nm NIF- 450/393 nm ISRA-446/360 nm	Tablets	NCD- 0.40 – 4.00 & 0.80 – 6.00 µg/mL NIF- 0.02 – 0.40 & 0.80 – 4.00 0 µg/mL ISRA- 0.1 0-0.90 & 1.00 – 9.00 µg/mL	LOD NCD- 0.0028 NIF- 0.017 ISRA-0.016 LOQ NCD- 0.0085 NIF- 0.050 ISRA-0.049	NCD- 0.9983 & 0.9999 NIF- 0.9903 & 0.9982 ISRA- 0.9997 & 0.9978	(44)
11	VRPHCl + DTZ HCl + NCDHCl + FLN	spectrofluorometric method 365 nm & 255 nm	Tablets	VRP HCl- 0.02-0.12 DTZ HCl- 0.01-0.06 NCD HCl- 0.02-0.12 FLN- 0.04-0.12	LOD & LOQ VRP HCl- 6.33 × 10-3 & 0.02 DTZ HCl- 3.1 × 10-3 & 0.01 NCD HCl- 2.93 × 1 0-3 & 9.76 × 10-3 FLN- 0.012 & 0.04	VRP HCl- 0.9998 DTZ HCl- 0.9998 NCD HCl- 0.9999 FLN- 0.9998	(45)

Liquid Chromatography-Mass Spectrometric Methods

Analytical Determination of NCD

An-Bang Wu et al. [52] Reported sensitive and simple liquid chromatography/electrospray mass spectrometry (LC-ESI-MS) method for determination of nicardipine. Nicardipine sample of 0.104M in methanol was exposed to a Philips 400WUV lamp under normal atmosphere. In a photochemical chamber, the sample was exposed to irradiation for 3hr, by analyzing the HPLC chromatogram. Chromatographically separation was achieved on Inertsil 5C18-AR-II Waters column (150 × 2.0mm i.d.) with CH_3CN-0.1M NH_4OAc in deionized H_2O (45:55v/v) as the mobile phase. UV recognition at 254nm. The flow rate were 0.2mL/min with injection volume 2µL [52].

Shin-ichi Kubo et al. [53] They developed simple extraction technique for utilize both GC-MS and LC-MS/MS using the same extracted sample (Table 5). Chromatographically separation was reached on Hypersil GOLD PFP column with mobile phase A- 0.1% formic acid in water mobile phase B- 0.2% formic acid in acetonitrile.

Table 5: LCMS analytical methods for NCD.

Sr.No	Drugs	Matrix	Extraction Method	Column	Mobile Phase	Linearity range/ FR	Ref
1	NCD	Pure form	Ammonium acetate	5C18-AR-II Waters column	CH3CN–0.1 M NH4OAc in deionized H2O (45:55, v/v)	FR-0.2 mL/min	(46)
2	NCD	Pure form	Lipid-removal and solid-phase extraction	Hypersil GOLD PFP column	Mobile phase A- 0.1% formic acid in water mobile phase B- 0.2% FA in acetonitrile	-	(47)
3	NCD + PIN +FLU+OXA+PRO+TRB+MP	Pure form	-	CHIROBIOTIC columns	70% B/30% A [B: 100% methanol containing 0.10% (by weight) ammonium trifluoroacetate; A: 100% methanol]	FR-1.2 mL/min	(48)

Bioanalytical Determination of NCD

Mingjie DENG et al. [54] Reported sensitive liquid chromatography/electrospray mass spectrometry (LC-ESI-MS) technique for the valuation of nicardipine nicardipine in rat plasma. Midazolam handed-down as interior standard, were initially extracted from plasma by a protein precipitation by acetonitrile. Method was established using a C18 column and separation was reached by a mobile phase containing acetonitrile-0.1% formic acid with gradient elution. The method was linear 5-1000ng/mL for nicardipine in rat plasma and correlation coefficient (R^2) were 0.996407. The flow rate were 0.4mL/min. The LOQ were found to 5ng/ml (Table 6). The intra- and inter-day variation was found to be less than 13%.

Table 6: LCMS bioanalytical methods for NCD.

Sr No	Drugs	Matrix	Extraction Methods	Column	Mobile Phase	Linearity range/FR	LOD/LOQ	Ref
1	NCD	Pure form	Protein precipitation by acetonitrile	SB-C18 (2.1 mm × 150 mm, 5 µm) column	ACN -0.1% FA	Linearity-5-1000 ng/mL FR- 0.4 mL/min	LOQ- 5 ng/mL	(49)
2	NCD	Tablet	Liquid–liquid extraction	C18 column	Methanol, water and FA (320:180:0.4, v/v/v)	Linearity-0.05–20.0 ng/mL FR - 0.6 ml/min	LOQ- 0.05 ng/ml	(50)
3	NCD	Pure form	Liquid–liquid extraction	Nucleosil C18 HD and XTerra MS C18	Ethanol /water 70:30	Linearity-1 to 500 or 1000 ng/mL FR - 0.4 ml/min	LOQ-0.5–2.5 ng/ml for plasma & 2–10 ng/ml for tissues	(51)
4	NCD	Pure form		ACQUITY UPLC BEH C18 column	ACN /5 mM ammonium acetate (7:3, v/v)	Linearity-1-500 pg/mL using 1 mL of plasma & 0.2-100 ng/mL using 20 mL FR - 0.2 mL/min	LOQ- 10 pg/mL	(52)
5	NCD	Pure form	solid-phase and liquid–liquid extractions	BEH C18 Column	ACN /water (1:1, v/v)	Linearity-1 pg/mL FR - 0.7 mL/min	LOQ-2 pg/mL	(53)
6	NCD	Pure form	Solid-phase extraction	Luna RP-C18 (2) analytical column	Solvent A (0.1% HCOOH, 1 mM NH4HCOO, pH 2.7) and solvent B (ACN / 0.1% HCOOH, 1 mM NH4HCOO, 75:25)	-	-	(54)
7	NCD	Pure form	Automated solid-phase extraction	C18 column	Solvent A (0.1% FA, 1mM ammonium formate, pH 2.7) and solvent B (acetonitrile–0.1% FA, 1 mM ammonium formate (95 : 5, v/v)	FR – 400 µl /min	LOD-1 ng/ml LOQ- 5 ng/ml	(55)
8	NCD	Pure form	-	MonoSpin C18 and C18-CX	0.1 mL MeOH containing 2% NH3	NCD-5-500 ng/mL	LOD- 2 ng/mL	(56)

Meiling Qi et al. [55] They reported LC-MS technique has been settled and validated for the analysis of nicardipine in human plasma. Method was established using a SB-C18 (2.1mm ×150mm, 5µm) column and mobile phase containing methanol, water and formic acid (320:180:0.4,v/v/v). The process was linear in series of 0.05-20.0 ng/ml for nicardipine. The relative standard deviations of inter -day and intra-day analysis for NC ≤9.3 and 11.1%, Respectively. The mean recovery of nicardipine ± 4.9%.

Katja Heinig et al. [56] Repoeted LC-MS-MS methods can be used successfully for the determination of a wide variety of pharmaceutical compounds in plasma and tissues. They performed analytical assay for a variety of substances including nicardipine, nitrendipine, felodipine and benzodiazepines. Method was developed using a Nucleosil C18 HD and XTerra MS C18 Column and separation was achieved by using a mobile phase containing Ethanol /water 70:30. Accuracy and precision were originated to be in the series of 84.4-119.1% and 1-16.5%, respectively. LOD were originated to be in the seriese of 0.5-2.5ng/ml for plasma and 2-10ng/ml for tissues.

Claudia A. Mueller et al. [57] Reported simple and selective liquid chromatography-mass spectrometry (LC/MS/MS) screening method is described for the screening of 11 calcium channel blockers of the 1,4-dihydropyridine type in human plasma. Chromatographic separation of the analyte was achieved on a a reversed-phase C18 column, gradient elution using a mobile phase of solvent A 0.1% formic acid, 1mM ammonium formate, pH 2.7 and solvent B acetonitrile-0.1% formic acid, 1mM ammonium formate (95:5 v/v) .

Voltammetric Methods

K. Zarei et al. [58] Implemented Stripping Voltammetric Purpose of Nicardipine Using β_Cyclodextrin Incorporated Carbon Nanotube. Modified Glassy Carbon Electrode. The method is linear above the series of 1.0×10^{-7} to 2.0×10^{-5}M with correlation coefficient $R^2 = 0.9982$. The LOD were calculated 1×10^{-8}M. The suggested technique was efficaciously regisred to the purpose of nicardipine more to the blood serum.

A.El. Jammal et al. [59] Implemented electrochemical behavior of several calcium antagonists of the dihydropyridine class by using a glassy carbon electrode. Both oxidation of the dihydropyridine ring and reduction of the nitro group have been pointed out using cyclic voltammetry. Splitting of the nitro group reduction peak occurs when the dihydropyridine ring is first oxidized. On the other hand, the reduction pathway of the nitro group depends on its position.

Joseph Wang et al. [60] Implemented cyclic voltametric performance of nicardipine using a carbon paste, glassy carbon and hanging mercury drop electrodes. Nlcardipine contains two redox centers , a reducible aromatjc nitro group and an oxidizable dihydropyridine ring (Table 7). The method is linear above the series of 1-5µg/ml. The LOD were calculated LOD: 8 x l0-8 M and 6 x l0-8 M (Figure 5).

Table 7: Voltammetric analytical methods for NCD.

Sr.No	Drug	Working Electrode	Linearity	LOD/LOQ	Technique	Ref
1	NCD	Glassy carbon electrode (GCE)	1.0×10^{-7} to 2.0×10^{-5} M	1×10^{-8} M	stripping differential pulse voltammetry	(57)
2	NCD	Mercury pool electrode (MPE)		-	polarography and cyclic voltammetry	(58)
3	NCD	Glassy carbon electrode (GCE)	0.1-5 ng/ml		Cyclic voltammetry	(59)
4	NCD	Glassy carbon electrode (GCE), platinum electrode (PE) or carbon paste electrode (CPE)			Differential pulse voltammetry	(60)
5	NCD	Glassy carbon electrode(GCE)			cyclic voltammetry	(61)
6	NCD	Glassy carbon, carbon (GCE) paste and hanging mercury drop Electrodes (PMDE , HMDE)	1-5 µg/ml	LOD- 8 x l0^{8} M & 6 x l08 M	Cyclic voltammetry	(62)
7	NCD	Mercury, glassy carbon, gold and platinum electrodes	-	LOD-4.8 ng/mL urine & 34 ng/mL Blood	Adsorptive stripping voltammetry & Differential pulse voltammetry	(63)

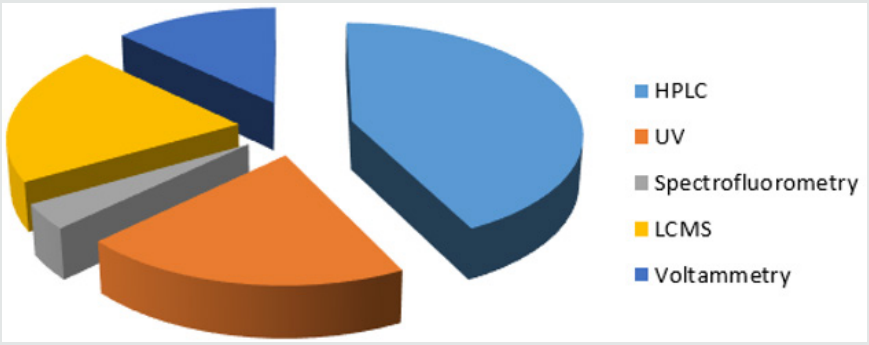

Figure 5: Percentage Utility of Analytical Approaches used for estimation of NCD.

Conclusion

The detailed review of the study high lights the current development of the analytical methods available for the quantification of NCD in bulk and pharmaceutical formulations and analysis of NCD in different matrices (such as plasma, serum, urine).A various investigation had perform including, HPLC, UV/Vis-Spectroscopy, Spectrofluorometry, LC-MS and electrochemical method. and a greater work of methods by high-performance

liquid chromatography and spectrophotometry were detected. The stability indicating assays have been developed for number of methods in the literature. The hyphenated LS-MS, LS-MS/MS method are reported for determination of VAL and its metabolite in plasma and other biological solutions. The aim of this article is to provide simple to use approaches with a correct scientific background to improve the quality of the analytical method development and validation process.

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