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Analytical Profile of Cinacalcet Hydrochloride: A Review

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Abstract

Cinacalcet Hydrochloride (CNA) is a drug used to treat both hyperthyroidism and hypercalcemia. Hyperthyroidism occurs due to the overproduction of thyroid hormones. Hyperthyroidism affects about 1.2% of US population. Similarly hypercalcemia is a condition where the calcium level in the blood will be above normal. Using a thorough computer assisted literature survey; this review article touches upon the reported analytical methods for the quantification of CNA both in API (Active Pharmaceutical Ingredient) and pharmaceutical dosage forms. The present write-up also encompasses the various published research articles like spectroscopic techniques, NMR studies, Electrophoretic methods, HPTLC and HPLC methods .This is the first review article in this series of the calcium sensing receptor agonist with focus on the analytical profile of CNA. In addition to these, hyphenated techniques involved in the estimation of CNA also discussed. Although, several methods were reported in the literature, HPLC stands out first for the quantification of CNA.

Keywords: Analytical methods, API, Cinacalcet hydrochloride, Hypercalcemia, Hyperthyrodism,

1. INTRODUCTION

Cinacalcet Hydrochloride (CNA) (Figure 1a,b,c) is a calcimimetic approved to treat secondary hyperparathyroidism in patients on dialysis for Chronic Kidney Disease (CKD) and hypercalcemia in patients with Parathyroid Carcinoma.[1].Cinacalcet Hydrochloride is N-[(1*R*)-1-naphthalen-1-ylethyl]-3-[3-(trifluoromethyl) phenyl] propan-1-amine;hydrochloride[2]. The molecular formula of CNA is $C_{22}H_{22}F_3N.HCl$ and its molecular weight is 393.87g/mol (HCl salt) and 357.41g/mol (as a freebase). It is white to off-white, crystalline solid and it is soluble in methanol, 59% ethanol, and slightly soluble in water. The pKa value of CNA is 8.72(10.3 –Strongest Base) and its melting point is 175–177°C. Due to the fact that R-CNA is around 75 times more active than its equivalent S-enantiomer, CNA has been widely adopted as a single R enantiomer.

Uncontrolled hyperparathyroidism (HPT), particularly HPT resulting from chronic kidney disease (CKD), is associated with significant morbidity and cardiovascular mortality. Traditional medical therapy (eg, vitamin D sterols, calcium, phosphate binders) has been inadequate for the management of HPT and its vascular and skeletal complications. CNA, a first-in-class calcimimetic, approved in both the United States and the European Union, offers a new therapeutic approach to the treatment of Secondary hyperparathyroidism (SHPT). CNA is a hydrochloride derived from equimolar amounts of cinacalcet and hydrogen chloride. It has a role as a calcimimetic and a P450 inhibitor. It derives from a cinacalcet. CNA is commercially available as the base and as the hydrochloride salt. This review article gives broad information to the readers about the various analytical methods available for the determination of CNA in pharmaceutical dosages forms and biological fluids. The current relevant analytical trends and prospective analytical methods for CNA have been presented and discussed. The CNA have been analyzed by various methods which have been described in different literatures. Among the reported analytical methods, HPLC was found to be the most developed and validated method for the estimation of CNA, followed by hyphenated systems, spectrophotometric and other methods (Figure 2).This review has become needful in view of the rapid progress in CNA research and development, its assay in both bulk and pharmaceutical dosage forms as well as their determination in biological fluids.

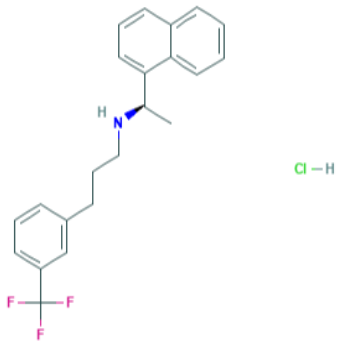

Figure 1(a) Structure of Cinacalcet hydrochloride

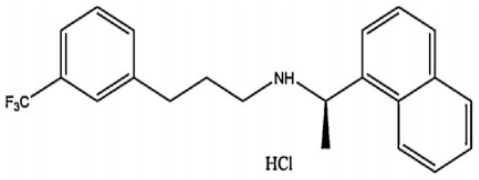

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Figure 1(b): R – Cinacalcet Hydrochloride

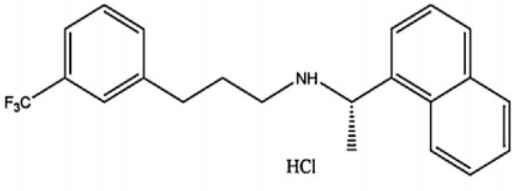

Figure 1(c) S – Cinacalcet Hydrochloride

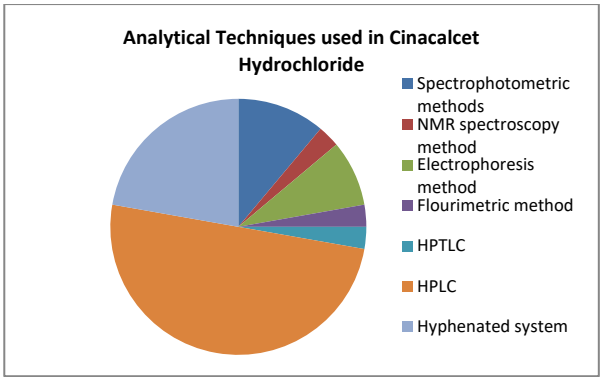

Figure 2: Distribution of analytical methods described in the literature for the determination of CAN

2. CINACALCET HYDROCHLORIDE

CNA is a calcimimetic that enhances the sensitivity of the parathyroid gland. Calcium-sensing Receptors (CaSR) to extracellular calcium, thus regulating parathyroid hormone secretion. This causes a decline in serum calcium and in parathyroid hormone secretion. Cinacalcet increases the sensitivity of calcium receptors on parathyroid cells to reduce parathyroid hormone (PTH) levels and thus decrease serum calcium level. In the prevention of secondary hyperparathyroidism in patients, CNA is taken orally. CNA is an oral medication used to treat secondary Hyperparathyroidism in dialysis patients with Chronic Kidney Disease [3]. The most often recorded adverse effects following administration include high or sluggish heart rate, muscle contractions, overactive reflexes, nausea, vomiting, or diarrhea, numbness or tingling sensations around the mouth, body pain, seizure, shortness of breath, swelling, a rapid increase in weight, stools that are bloody or tarry, spitting up blood. [4]. CNA is often contraindicated in hypocalcemia.

3. ANALYTICAL TECHIQUES FOR THE DETERMINATION OFCNA

According to literature review, many chromatographic and spectrophotometric methods for the determination, quantification, stability indication and separation of CNA in formulation, bulk, and biological fluids have been developed. Impurity determination was also carried out. HPLC, HPTLC, UV-Visible spectroscopic techniques, LC – Hyphenated system, Electrophoresis, Flourimetry and NMR spectroscopy were among the techniques used in the experiments.

4. SPECTROSCOPIC METHODS

Spectrophotometric instruments are one of the most robust instrumental techniques of pharmaceutical analysis for qualitative and quantitative analysis of drug; due to easy, economical, and accurate analysis.A.Manjulaet.al., developed and validated UV and colorimetric methods for the determination of CNA in the bulk drug substance and in its pharmaceutical formulations [5]. Amruta. B. Loni et al., [6] developed two methods to determine CNA by spectrophotometry. Method A used absorbance maxima method, which is based on the measurement of absorption at maximum wavelength, 281.0 nm. Method B used Area under Curve (AUC), in the wavelength range of 249-299 nm.Darwish et al, developed a novel spectrophotometric method for determination of CNA in its tablet dosage forms. The study was conducted to investigate the reaction between CNA and 1, 2-naphthoquinone-4-sulphonate (NQS) reagent [7]. Malligarjuna Rao N et al., developed a stability indicating UV spectro-photometric method for the estimation of CNA in bulk and tablet dosage form [8]. The studies conducted are depicted in Table 1.

Table 1: Analytical methods described in the literature for determination of CNA by spectrophotometric analysis

Title	Method	Wavelength	Description	Reference
Spectrophotometric determination of CNA in bulk and its dosage form	UV-Visible Spectrophotometry	UV – 271nm Colorimetry – 546nm	UV – validated in terms of linearity and stability Colorimetry – validated in terms of linearity, ruggedness and robustness	[5]
Spectrophotometric estimation of CNA in bulk and tablet dosage form	Visible spectrophotometry	Method A -281nm Method B -249-299 nm	Method A – Absorbance maxima method Method B – Area Under the Curve Validated in terms of specificity, linearity, recovery, accuracy and precision	[6]
Novel spectrophotometric method for determination of CNA in its tablet via derivatisation with 1, 2 naphthoquinone- 4 sulphonate	Visible-spectrophotometry	490 nm	The stoichiometry and kinetic of the reaction were investigated and the reaction mechanism was postulated. This color-developing reaction was employed in the development of a simple and rapid visible-spectrophotometric method for determination of CNA in its tablets	[7]
Development and validation of novel stability indicating UV spectrophotometric method for the estimation of CNA in bulk and tablet dosage form	UV Spectrophotometry	281nm	The parameters linearity, precision, accuracy, limit of detection and limit of quantitation were studied according to International Conference on Harmonization guidelines. Forced degradation studies were conducted under various conditions.	[8]

Table 2: Application of NMR procedures for the determination of CAN

Title	Method	MHz used	Description	Reference
Performance of new 400-MHz HTS power-driven magnet NMR technology on typical Pharmaceutical API, CNA	NMR spectroscopy	9.4T (400 MHz)	Chose Cinacalcet Hydrochloride (HCl) as a typical API and acquired 1D and 2D homonuclear and heteronuclear standard NMR experiments (1D 1 H, 1D 13C, 2D 1 H–1 H COSY, 2D 1 H–1 H NOESY, 2D 1 H–13C HSQC, and 2D 1 H–13C HMBC) normally used for structure elucidation, these results clearly indicate that new magnet technology works with existing parameter sets and pulse programs and provides comparable results with standard NMR instruments	[9]

5. Nuclear Magnetic Resonance Spectroscopy Method

In the academic and pharmaceutical industries, Nuclear Magnetic Resonance (NMR) is used to quantify and characterize pharmaceuticals. Maria Victoria et al, tested and compared performance of new 400-MHz HTS power-driven magnet NMR technology to a standard NMR instrument using CNA as typical API [9]. Specification of the experiment is listed in the Table 2.

6. Electrophoresis Analysis

There were few reported analytical methods of CNA using electrophoresis technique. B. Pasquini et al., developed capillary electrophoresis method for the simultaneous determination of the enantiomeric purity and of impurities of the chiral calcimimetic drug CNA based on Quality by Design principles [10].M. Al Shehri et al., proposed a validated stability-indicating capillary electrophoresis method for the determination of CNA using a photodiode array detector at 220 nm [11]. Development for the chiral separation of R, S CNA was performed using Capillary Zone Electrophoresis method by Ginterová P et al [12]. The analysis methods are demonstrated in the Table 3.

7. Fluorimetric Method

Darwish et al., created and validated a highly sensitive fluorimetric system for measuring CNA in tablets and plasma. In an alkaline buffered form, CNA was nucleophilically substituted with 7-chloro-4-nitrobenzoxadiazole at pH 9 [13]. Method is demonstrated in Table 4.

Table 3: Electrophoresis methods for the determination of CNA

Title	Objective	Evaluation	References
Chiral Capillary Zone Electrophoresis in enantio separation and analysis of CNA impurities : use of Quality by Design principles in method development	Capillary Electrophoresis method for the simultaneous determination of the enantiomeric purity and of impurities of CNA using Quality by Design principles	Method for enantio separation and impurity assay of CNA using Capillary Electrophoresis was developed. Method development was carried out by Quality by Design approach. Organic solvent-modified CZE was selected as separation system.	[10]
Determination of CNA by Capillary Electrophoresis with photodiode assay detection	Capillary Electrophoresis method using a photo- diode array detector at 220 nm for the determination of CNA	Method determination of CNA in bulk and pharmaceutical formulations were done	[11]
Enantiomeric purity control of R – CNA in pharmaceutical product by Capillary Electrophoresis	Method was applied to the analysis of tablets containing R-CNA as the active substance.	Method determined 0.1 % of S-CNA in tablets containing R-CNA as the active substance.	[12]

Table 4: Fluorimetric Method

Title	Objective	Evaluation	Reference
A highly sensitive fluorimetric method for determination of CNA in tablets and plasma via derivatization with 7-chloro-4-nitrobenzoxadiazole	Determination of Cinacalcet Hydrochloride in tablets and in plasma based on nucleophilic substitution reaction	Kinetics of the reaction, stoichiometry, mechanism were determined	[13]

Table 5: Analytical conditions for methods by planar chromatography

Title	Method	Mobile phase	Stationary phase	Wavelength	Reference
Determination and validation of HPTLC method for CNA	HPTLC	Chloroform: acetonitrile (6:4, v/v)	Aluminum-backed silica gel 60 F254 plates (10 × 10 cm)	282 nm	[14]

Table 6: Reported HPLC methods of CNA

Title	Method	Mobile phase	Stationary phase	Wavelength	Reference
Development and Validation of a RP-HPLC method for the quantitative estimation of CNA in tablet dosage form.	RP – HPLC	Methanol and phosphate buffer (pH 6.8) in the ratio 60: 40 v/v	C_{18} column	232nm	[15]
Development and validation RP-HPLC method for estimation of CNA in bulk and tablet dosage form,	RP- HPLC	Methanol, acetonitrile, and water in the ratio of 70:15:15	Inertsil ODS C_{18}	280nm	[16]
Content determination of CNA Hydrochloride tablets by HPLC,	HPLC	Triethylamine solution (pH 8)– Methanol (15:85)	Phenomenex C_{18} column	272 nm	[17]
Validated RP-HPLC method for the estimation of CNA in bulk and tablet dosage form.	RP – HPLC	Water: methanol: acetonitrile (20:60:20v/v/v)	Inertsil ODS C_{18} column (15 cm;4.6 mm; 5 µm)	235 nm	[18]
Development and validation of a quantitative assay for the determination of CNA and its main metabolites in human plasma using RP-HPLC method	RP – HPLC	Acetonitrile, methanol, and 50 Mm Phosphate buffer (40:20:40 v/v)	Isocratic mode on Kinetex C_{18} 100 Å	360, 345, 395, 480, and 495 nm	[19]
A highly sensitive HPLC method with non-extractive sample preparation and UV detection for trace determination of CNA in human plasma	HPLC	Acetonitrile and 50 mM Phosphate buffer (50:50 v/v)	Isocratic mode on a C_{18} column (150 mm × 4.6 mm, i.d. 5µm)	235 nm	[20]
A new validated liquid chromatographic method for the determination of impurities in CNA	LC	Potassium dihydrogen phosphate buffer mixed with 1.0 ml of triethylamine, adjusted to pH 6.0 with phosphoric acid and acetonitrile	C_{18} (250 × 4.6 mm, 5µ) column	223 nm	[21]
Development and validation of stability Indicating RP-HPLC Method for the Estimation of CNA in bulk and their formulations	RP- HPLC	Phosphate buffer: acetonitrile (40:60 v/v) pH adjusted to 3.0 ±0.05 with diluted ortho-phosphoric acid	X-Terra Symmetry C_{18} (4.6 ×150mm; 5 µm)	282 nm	[22]
Stability indicating HPLC method for the Estimation of CNA API	HPLC	Methanol: water (70:30v/v) pH adjusted to 3.6 with dilute orthophosphoric acid	Phenomenex C_{18} column (150 mm×4.6 mm, 5.0 µm)	271 nm	[23]
Stability-indicating RP-HPLC method for the quantitative analysis of CNA in tablet dosage form	RP – HPLC	0.2% Triethylamine in water (pH 6.5 with orthophosphoric acid) and Methanol (20:80)	C_{18}, (25 cm×4.6 mm,5 µm)	225 nm	[24]
A validated chiral LC method for the enantiomeric separation of CNA	Chiral LC	n-Hexane, ethanol and trifluoroacetic acid(95:5:0.1, v/v)	Chiralpak-IA column (250 × 4.6 mm, particle size 5 µm)	223 nm	[25]

Title	Method	Mobile phase	Stationary phase	Wavelength	Reference
Chiral chromatography studies of chemical behavior of CNA on polysaccharide chiral reverse phase HPLC stationary phase	Chiral RP – HPLC	10mM triethylamine (pH 8) –acetonitrile (40:60)	Chiralpak AY (amylose 5-chloro-2-methyl phenyl carbamate chiral stationary phase	224 nm	[26]
Enantio separation of CNA and its two related compounds by HPLC with self-made chiral stationary phases and chiral mobile phase additives	Chiral HPLC	n-Hexane along with different percentages of various alcohols	VAN (5 µm, 250 mm×4.6 mm id), 1-Na-VAN column (5 µm, 250 mm4.6 mm id) and CDMPC (5 µm, 250 mm4.6 mm id)	254nm	[27]
Method development and validation and degradation studies for CNA drug by RP-HPLC method,	RP – HPLC	Orthophosphoric acid: methanol (30:70)	Agilent Zorbax C18 (25 cm×4.6 mm, 5 µm)		[28]
Separation and quantitative determination of CNA metabolite in urine sample by using RP-HPLC after derivation with fluorescent labeling reagent	RP- HPLC	Acetate buffer (pH 3.5):methanol (30:70 v/v)	Microsorb-MV 100-5 C_{18}column (250 × 4.6 mm, 5 µm)	290, 335, 395, and 405 nm	[29]
Development and validation of stability indicating RP-UPLC method for the estimation of impurities in CNA hydrochloride API and its Formulations	RP – UPLC	pH 6.6 Phosphate buffer and acetonitrile	Acquity BEH Shield RP18, 100 × 2.1 mm, 1.7 µm column	223 nm	[30]
Indirect reversed-phase high-performance liquid chromatographic and direct thin-layer chromatographic enantio resolution of (R,S)-CNA	Indirect RP-HPLC and direct TLC	HPLC: Aqueous TFA (0.01 M)–acetonitrile in a linear gradient of acetonitrile from 30 to 65% as mobile phase TLC : Acetonitrile–MeOH–H_2O as mobile phase	HPLC : Waters Spherisoro ODS (250 x 4.6 mm i.d., 5 mm) column TLC : silica gel as stationary phase	340nm	[31]

8. CHROMATOGRAPHIC TECHNIQUES

8.1. High performance thin layer chromatography (HPTLC) method

Kamatham S et al., developed and validated a novel and simple High-Performance Thin – Layer Chromatographic (HPTLC) method for the analysis of CNA in API [14].The detailed information is depicted in Table 5.

8.2. High Performance Liquid Chromatography Method

HPLC is one of the most widely used instrumental analytical methods for solving pharmaceutical research problems, both in academics and in industry. Various methods have been developed and validated using different stationary phases and mobile phases for the estimation of CNA. Debadash panigrahi et al [15], N.S. Ganesh et al [16], L. Zhao et al [17], R. Tekula et al [18], Amir Farnoudian habibi et al [19] developed and validated methods for the estimation of CNA. Darwish et al [20] developed and validated a highly sensitive High Performance Liquid Chromatographic method with non-extractive sample preparation and Ultraviolet detection for the trace determination of CNA in human plasma. Paracetamol was used as the internal standard. CNA and paracetamol were isolated from plasma by protein precipitation with acetonitrile. A.Sigala et al [21] developed and validated a reversed-phase High Performance Liquid Chromatographic method for the determination of CNA and its impurities. N M Rao et al [22], K. Manikandan et al [23], developed and validated a stability indicating Reverse Phase High Performance Liquid Chromatographic method for the estimation of CNA in bulk and formulations, in API respectively. H.H.T. Dugga et al [24] developed stability indicating RP-HPLC method for the estimation of CNA in tablet dosage form. V. Ravinder et al [25], M. Dousa et al [26], Canyu Yanga et al [27] developed chiral HPLC for the

enantio separation of CNA, for the study of chemical behavior of CNA on polysaccharide chiral stationary Phase, for the enantio separation of CNA, and its two related compounds using self-made chiral stationary phase and mobile phase, respectively. E.R. Bammidi et al [28] prepared a method and validated CNA including degradation study. Amir Farnoudian Habibi et al [29] researched on separation and quantitative determination of CNA metabolite in urine sample by using RP- HPLC after derivation with fluorescent labeling reagent. P. S. Reddy et al [30] developed and validated a stability indicating RP-UPLC method for the estimation of impurities in CNA in API and its formulations. An indirect Reversed-Phase High-Performance Liquid Chromatographic and direct Thin-Layer Chromatographic enantio resolution of (R,S) – CNA was performed by R. Bhushan et al [31]. Studies are demonstrated in Table 6.

9. HYPHENATED SYSTEM

The hyphenated methods are a complex, repeatable technique and adaptable method for estimating analytes from a broad range of biological and medicinal samples. Nirogi R et al [32] developed a method for the quantification of CNA using LC – MS/MS and Liquid – liquid extraction from 50µl of plasma.LC – Tandem mass spectrometry was used by Yang F et al [33] to determine CNA in human volunteers. R. N. Rao et al [34] developed liquid chromatography for separation and determination of CNA and ESI – MS/MS, FTIR, and NMR characterization were used for the forced degradation product of CNA micro method for quantification of CNA in human plasma by LC – Tandem Mass spectrometry using a stable isotope – labeled internal standard was developed by G. Cangemi et al [35]. An improved LC – MS/MS method for determination of CNA in human plasma and its application of food intake effect on the pharmacokinetics of CNA in healthy volunteers was performed by Li L et al [36]. N.R. Ramisetti et al [37] used LC – MS/MS for the determination of CNA enantiomers in rat plasma using chirobiotic V column in polar ionic mode. T.A. Wani et al [38] developed a highly sensitive and simple validated ultra-performance liquid chromatography/tandem mass spectrometry method for the determination of CNA in human plasma. S. Reddy et al [39] validated a LC-MS/MS method for the estimation of CNA in human plasma. Experiments are demonstrated in the Table 7.

Table 7: Hyphenated techniques for the determination of CNA in biological samples

Title	Method	Mobile phase	Stationary column	Evaluation	Reference
Quantification of CNA by LC – MS/ MS using Liquid – liquid extraction from 50µl of plasma	LC – MS/MS using liquid – liquid extraction	Ammonium acetate adjusted to pH 4.0 with diluted formic acid and acetonitrile (5:95, v/v)	Waters Symmetry C18 4.6 × 100 mm^2, 3.5 µm	Applied to quantify CNA concentrations in a preclinical pharmacokinetic study after a single oral administration of CNA at 10 mg/kg to rats	[32]
Determination of CNA in human by LC – Tandem mass spectrometry	(HPLC–MS/MS)	Acetonitrile–water–formic acid (90:10:1)	Inertsil SIL-150 (2.1 mm × 50 mm, 5 µm)	Applied to a pharmacokinetic study of CNA hydrochloride in healthy chinese volunteers	[33]
Liquid chromatography separation, determination and ESI – MS/MS, FTIR, and NMR characterization of the forced degradation product of CNA	HPLC, ESI – MS/MS, FTIR, and NMR	10 mM aqueous ammonium acetate-acetonitrile	Phenomenex C-8 (250 × 4.6 mm, 5 mu m)	Applied not only to quantify the degradation products but also to quantify process related substances of CNA in bulk drugs. The forced degradation of CNA was carried out under acidic, basic, thermal, photo, and peroxide conditions, and the degradation products were isolated and characterized by ESI-MS/MS, FT-IR, ^1H and ^{13}C NMR spectroscopy.	[34]
Micromethod for quantification of CNA Hydrochloride in human plasma by LC – Tandem Mass spectrometry using a stable isotope – labeled internal standard	LC – Tandem Mass Spectrometry	0.1% formic acid in water and mobile phase B of 0.1% formic acid in methanol	Thermo Scientific hypersil Gold C_{18} column (50 mm · 2.1 mm, internal diameter 1.9 mm; Thermo Fisher Scientific, Inc, Waltham, MA)	The method provides high specificity, precision, and accuracy for rapid quantification of CNA plasma concentrations, and it is suitable for application in pediatric PK studies	[35]

An improved LC – MS/MS method for determination of CNA in human plasma and its application of food intake effect on the pharmacokinetics of CNA in healthy volunteers	LC – MS/MS	Mobile phase A water (containing 0.1% formic acid) and the mobile phase B of acetonitrile–water (95:5, v/v) (containing 0.2% formic acid)	C_{18} column	Based on liquid–liquid extraction and cinacalcet-d4 was used as an internal standard. applied to a pharmacokinetic description of oral dose of CNA and the significant effect of food intake on the pharmacokinetics of CNA	[36]
LC – MS/MS determination of CNA enantiomers in rat plasma on chirobiotic V column in polar ionic mode: application to pharmacokinetic study	LC – MS/MS	2.5 mm ammonium formate in 100% methanol was used as the mobile phase	Chirobiotic V column packed with vancomycin as a chiral stationary phase	Applied to study the pharmacokinetics after a single dose by oral administration of 10 mg/kg of CNA enantiomers to healthy male wistar rats	[37]
Highly sensitive and simple validated ultra-performance liquid chromatography/tandem mass spectrometry method for the determination of CNA in human plasma	UPLC-Tandem mass spectrometry	Acetonitrile:10mM ammonium acetate: formic acid (90:10:0.1%)	C_{18}Acquity UPLC BEH^{TM} column	Used for analysis of CNA in human plasma	[38]
A validated LC-MS/MS method for estimation of CNA in human plasma	LC-MS/MS	5 mM ammonium acetate (pH 40.2):acetonitrile (40:60)	SCX column (5 cm×4.6 mm; 5 µm)	Applied for estimation of CNA during biostudies.	[39]

10. CONCLUSION

CNA is an effective medication use for the treatment of secondary hyperparathyroidism in patients on dialysis for Chronic Kidney Disease (CKD) and hypercalcemia in patients with parathyroid carcinoma. This review is targeted at outlining the various analytical methods and other related aspects of CNA. The analytical profile of the drug highlights various analytical methods for the determination of CNA in API, formulation and biological fluid. HPLC was found to be the most developed and validated method for the estimation of CNA, followed by hyphenated systems, spectrophotometric methods. It is however pertinent to state that newer analytical methods are being developed with respect to advancing technology and this may necessitate a future review.

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