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A Review on Methods for Simultaneous Determination of Nitrendipine and Hydrochlorothiazide

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ABSTRACT

: Analytical chemistry is a branch of chemistry that focuses on the qualitative and quantitative separation of substances, samples, and mixtures into their component constituents. Pharmaceutical analysis is crucial to the assessment of pharmaceutical formulations for quality assurance and control. The development of analytical methods and analytical instruments has improved, which has decreased analysis time and cost and increased precision and accuracy. These techniques were utilized by reputable laboratories to examine the performance, purity, safety, identity, and efficacy of drug items. Validation is the process of gathering and analyzing data from the process design stage through commercial production to create scientific proof that a process can reliably produce high-quality goods. In this review we are discussing some methods for simultaneous determination of hydrochlorothiazide and nitrendipine.

INTRODUCTION

I. Hydrochlorothiazide

Hydrochlorothiazide is a diuretic medication often used to treat high blood pressure and swelling due to fluid buildup. Other applications include the treatment of renal tubular acidosis and diabetes insipidus, as well as lowering kidney stone risk in people with high urine calcium levels. Hydrochlorothiazide is less effective than chlorthalidone for prevention of heart attack or stroke (1) Hydrochlorothiazide is taken by mouth and may be combined with other blood pressure medications as a single pill to increase effectiveness. Hydrochlorothiazide is less effective than chlorthalidone for prevention of heart attack or stroke (19) (20).

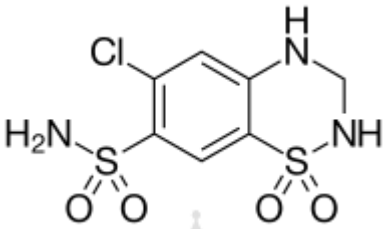

Figure 1: Chemical structure of the hydrochlorothiazide

1. Chemical and physical data

- Formula: $C_{18}H_{20}N_2O_6$
- Molar mass: 360.366 g·mol^{-1}
- Melting point 156-160 °
- Solubility: DMSO 72 mg/mL; Water <1 mg/mL
- Absorption maxima: 235nm

2. Pharmacokinetic data

- Bioavailability: 60–70%
- Protein binding: 98%
- Metabolism: Hepatic (completely)
- Onset of action: 1–2 hours

- Elimination half-life: 8–24 hours
- Excretion: Urine (30%)

3. Mechanism Of Action Of Hydrochlorothiazide

The distal convoluted tubule cannot transfer sodium chloride because of hydrochlorothiazide. The kidney then excretes more salt along with liquids. After an oral dose, pharmacological effects start to take effect in about two hours, peak in four hours, and persist for around six to twelve hours. The bulk of hydrochlorothiazide is eliminated in the urine unaltered since it is not metabolised. Bicarbonate and potassium are also lost as a result.

It is unclear exactly how hydrochlorothiazide works to lower blood pressure over the long run. The medication does lower blood pressure when given immediately because it encourages diuresis and reduces plasma volume. Hydrochlorothiazide, however, seems to be lowering blood pressure by lowering peripheral resistance after prolonged administration. It is unknown how the medication works to dilate blood vessels, although laboratory data points to potential mechanisms include inhibition of the carbonic anhydrase enzyme, desensitisation of calcium-sensitive smooth muscle receptors, and inhibition of kidney autoregulation (2).

4. Medical uses

- Hydrochlorothiazide is a medication that is used to treat a number of conditions, including hypertension, congestive heart failure, symptomatic emphysema, diabetic insipidus, and renal tubular acidosis. In people whose urine contains a lot of calcium, it is also used to avoid kidney stones (3).

- When compared to monotherapy, the combination of fixed-dose medications such as losartan and hydrochlorothiazide has the added benefit of a more potent antihypertensive effect and additional antihypertensive efficacy at the dose of 100 mg/25 mg (16) (17).

- In addition to treating hypercalciuria, Dent's disease, Ménière's illness, and hypoparathyroidism, (18) hydrochlorothiazide is also occasionally used to prevent osteopenia.

II. Nitrendipine

- Nitrendipine is a dihydropyridine calcium channel blocker. It is used in the treatment of primary essential hypertension to decrease blood pressure and can reduce the cardiotoxicity of cocaine (4). It received medical use approval in 1985 after being patented in 1971. (22).

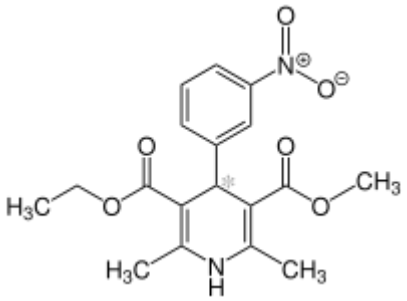

Figure 2: Chemical structure of nitrendipine

1. Chemical and physical data

- Formula: $C_{18}H_{20}N_2O_6$
- Molar mass: 360.366 g·mol^{-1}
- Melting point: 156-160 °C
- Solubility: DMSO 72 mg/mL; Water <1 mg/mL
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2. Pharmacokinetic data

- Bioavailability: 60–70%
- Protein binding: 98%
- Metabolism: Hepatic (completely)
- Onset of action: 1–2 hours
- Elimination half-life: 8–24 hours
- Excretion: Urine (30%)

3. Mechanism Of Action Nitrendipine

Nitrendipine enters the body through the mouth, where it is absorbed by the gut and processed by the liver before reaching the smooth muscle and cardiac muscle cells in the systemic circulation. Since its resting membrane potential is lower, it binds L-type calcium channels in smooth muscle cells more efficiently (5). The nitrendipine diffuses through the membrane and attaches to its high affinity binding site on the inactive L-type calcium channel, which is situated between each of the 4 intermembrane components of the 1 subunit (5) thought to have domain-interface model of binding. Nitrendipine binds to L-type calcium channels in hypertension, reducing the likelihood that they will be open and lowering calcium inflow. These muscle cells cannot contract smoothly because of the low calcium levels. Smooth muscular dilatation is made possible by avoiding muscle contraction. Vascular dilation lessens overall peripheral resistance, which eases the strain on the heart and prevents scarring or heart failure.

4. Medical uses

- Patients with hypertension receive nitrendipine in the form of daily 20 mg oral pills (6). With this dosage, blood pressure can be lowered by 15-20% within 1-2 hours after administration. In older patients, a lower dosage of up to 5 mg/day may be similarly effective (this reduction in medication quantity is attributable to diminished liver function or "first pass" metabolism); the dosage may increase to as much as 40 mg/day with long-term therapies. Nitrendipine is absorbed into the blood after being digested and binds to plasma proteins there. The vast majority (98%) is linked to plasma proteins, as are 70–80% of its inactive polar metabolites. In the first 96 hours after hepatic metabolism, 80% of the 20 mg dose can be retrieved as inactive polar metabolites. The drug's precise volume of distribution is 2–6 L/kg. Nitrendipine has a medication half-life of between 12 and 24 hours. There have been reports of headaches, flushing, edema, and palpitations as side effects. The vasodilator action of this medication is responsible for all of these side effects. (6).

- Individuals with hypertension receive 20 mg oral tablets of nitrendipine daily. With this dosage, blood pressure can be lowered by 15-20% within 1-2 hours of administration. In elderly people, a lower dosage of up to 5 mg/day may be similarly effective (this reduction in medication quantity is attributed to impaired liver function or "first pass" metabolism) (21). The dosage may increase to as high as 40 mg/day with long-term therapies.

III. Literature review:

- **Attalal et al (**2021) demonstrated Advanced eco-friendly UV spectrophotometric approach for resolving overlapped spectral signals of antihypertensive agents in their binary and tertiary pharmaceutical dosage form This study introduces brand-new, environmentally friendly spectrophotometric techniques for the simultaneous examination of the pharmaceutical dosage forms of amlodipine (AML), telmisartan (TEL), hydrochlorothiazide (HCTZ), and chlorthalidone (CLO). For the simultaneous determination of a binary mixture of TEL and CLO in TELMIKIND-CT 40 tablets and a tertiary mixture of AML, TEL, and HCTZ in TELVAS 3D 80 mg tablets, Fourier-self deconvolution, amplitude factor, and first derivative approaches were recommended (7).

- **Binh et al** (2021) Simultaneous Determined Hydrochlorothiazide and Losartan Potassium in Pharmaceutical Product by UV-Vis Spectrophotometric Method with Kalman Filter Algorithm. At 1.0 nm intervals, spectra of the standard and sample solutions were recorded in the 220 to 300 nm wavelength region. The concentrations of HCT and LSP in the sample solutions were determined using the Kalman filter algorithm, which was created on the Microsoft Excel 2016 and Visual Basic for Applications (VBA) platform. The accuracy and consistency of measurements when assessing HCT and LSP in the Splozarsin Plus tablet and comparing the mean values of their contents in the sample with those evaluated using HPLC were utilised to establish the technique validation. The proposed method is simple and less expensive than the traditional HPLC methodology (8).

- **Mohammad et al** (2021) demonstrated the Simultaneous determination of enalapril maleate and nitrendipine in tablets using spectrophotometric methods manipulating ratio spectra. For the simultaneous assessment of EN and NT in combined medicinal dose form (Eneas® tablets), a reliable spectrophotometric approach utilising ratio spectra was devised and validated. First derivative ratio spectrophotometric method (1DD) was used to determine EN and NT, with amplitude maxima measured at 219.2 nm and 233.4 nm, respectively. In the second approach, ratio difference spectrophotometry, the amplitude differences between 213 and 225 nm on the ratio spectrum of EN and 241 and 227 nm on the ratio spectrum of NT were used to estimate EN and NT (9).

- **Padh et al** (2018) developed and validated Q-absorbance ratio spectrophotometric method for simultaneous estimation of mangiferin and berberin hcl in bulk and synthetic

mixture. The US FDA patent is approved for fixed dosage combination of Mangiferin (MF) and Berberin HCl (BER) as antidiabetic herbal formulation. Absorbance ratio method uses the ratio of absorbances at two selected wavelengths, one which is an iso-absorptive point and other being the λmax of one of the two components. From the overlay spectra of two phytomarkers, it is evident that MF and BER show an iso-absorptive point at 317 nm. The second wavelength used is 257 nm, which is the λmax of MF. The drug response with respect to absorbance was linear over the concentration range 5 - 30 µg/ml for MF and 10 - 60 µg/ml for BER. The percentage recovery of MF and BER as found to be 100.00% and 100.07% respectively. The method can be successfully employed for the simultaneous determination of MF and BER in pharmaceutical formulations. The developed method is validated as per ICH guideline Q2 (R1) (10).

- **Shalan et al** (2019) performed the Simultaneous evaluation of losartan and amlodipine besylate using second derivative synchronous spectrofluorimetric technique and liquid chromatography with time-programmed fluorimetric detection. This study is concerned with two sensitive, fast and reproducible approaches; namely, second-derivative synchronous fluorimetry (method I) and reversed phase high-performance liquid chromatography with fluorimetric detection (method II) for synchronized evaluation of losartan (LOS) and amlodipine besylate (AML). Method I is based on measuring second derivative synchronous fluorescence spectra of LOS and AML at Dl ¼ 80 nm in water. The experimental factors influencing the synchronous fluorescence of the considered compounds were sensibly adjusted. The study was extended to the evaluation of the two drugs in their co-formulated tablets (11).

- **Shrivastava et al.** (2018) demonstrated the Key Aspects of Analytical Method Development and Validation. Development of a method is crucial for discovery, development, and analysis of medicines in the pharmaceutical formulation. Method validation could also be thought to be one in all the foremost well-known areas in analytical chemistry as is reproduced within the substantial variety of articles submitted and presented in peer review journals every year. Validation of an analytical procedure is to demonstrate that it's appropriate for its intended purpose. Results from method validation are often wont to decide the quality, reliability and consistency of analytical results. Analytical methods need to be validated or revalidated. This review describes general approach towards validation process and validation parameters to be considered during validation of an analytical method. It also refers to various regulatory requirements like WHO, USFDA, EMEA, ICH, ISO/IEC.

The parameters described here are according to ICH guidelines which include accuracy, precision, specificity, limit of detection, limit of quantification, linearity range and robustness (12).

- **Kamra et al.** (2017) developed and validated a new simultaneously method for estimation of resveratrol and benzoyl peroxide by UV spectrophotometric method. A new simple, sensitive, spectrophotometric method in UV region has been developed for the simultaneous estimation of benzoyl peroxide and resveratrol. The method involved absorption subtraction method using two wavelengths, with one being of benzoyl peroxide (234 nm,) and the other being the isoabsorptive point of both drugs (246 nm). The Standard solution of benzoyl peroxide and resveratrol shows maximum absorbance at 234 nm and 306 nm respectively. Beer's Lamberts law is obeyed in concentration range 1-7 µg/ml for resveratrol while for benzoyl peroxide, Beer's Lambert law is obeyed in concentration range 1-10 µg/ml. The results of analysis have been validated statistically and by recovery study. The accuracy ranged for resveratrol was between 103.16 and 104.49% and for benzoyl peroxide 104.05 to 110.49. The method was found to be precise, reproducible and rapid (13).

- **Kamal et al.** (2016) reviewed the UV spectrophotometric methods for simultaneous multicomponent analysis. In present era, market is floated with various combinations dosage forms and the number is increased day by day. These multicomponent formulations are gaining interest due to greater patient acceptability, increased potency, multiple action, fewer side effects, and quicker relief. Therefore, it is desired that these formulations meet the entire standards related to their quality, safety, and efficacy. This can only be possible if different analytical techniques are available for their determination. Different UV spectrophotometric methods are used in simultaneous multicomponent analysis. Such methods are based on recording and mathematically processing absorption spectra. This review is mainly focused on simultaneous equation method, difference spectrophotometry, derivative spectrophotometry, absorbance ratio spectra, derivative ratio spectra, double divisor ratio spectra derivative method, successive ratio - derivative spectra, Q-absorbance ratio method, isosbestic point method, absorptivity factor method, dual wavelength method, ratio subtraction method, mean centering of the ratio spectra, absorption factor method and multivariate methods. An overview of theories and some applications of these methods are presented (14).

- **Shang d et al. (2011)** For the simultaneous measurement of nitrendipine and hydrochlorothiazide in spontaneously hypertensive rat (SHR) plasma, an HPLC technique with on-line solid phase extraction (SPE) and DAD detection was devised. 100 L of plasma samples were directly loaded onto a CAPCELL MF C8 SPE column. By using on-line SPE technology, high-abundance proteins and the majority of plasma's matrix components were eliminated, and nitrendipine and hydrochlorothiazide that had been trapped on the SPE column were successfully separated on a C18 analytical column. The temperature in the column was kept constant at 20 °C. For NTDP and HCTZ, the ideal detection wavelength was 237 nm, respectively. The duration of the analytical run was 34 minutes. For nitrendipine and hydrochlorothiazide, the proposed technique was linear over the ranges of 5-500 ng mL1 and 10-1000 ng mL1, respectively. During the validation period, the method's sensitivity and precision fell within allowable bounds. The technique proved effective in examining the pharmacokinetic properties of nitrendipine and hydrochlorothiazide in rats with spontaneous hypertension. (15)

- **Mohammad et al. (2020)** for the simultaneous determination of ENA, ENAT, NIT, DNIT, and HCT in human plasma, a sensitive, accurate, and exact LC-MS/MS method was created and validated. One-step PPT was used for sample preparation; it was quick and easy to use, and it produced good recovery results. Utilising an isocratic elution technique on a UPLC column connected to a tandem mass spectrometer decreased the run time. With excellent selectivity and sensitivity, the suggested approach might quickly identify a significant number of co-administered cardiovascular medications in human plasma. The LLOQs for ENA, ENAT, NIT, HCT, and DNIT were 1 ng/mL, 20 ng/mL, 5 ng/mL, and 2 ng/mL, respectively. This shows that the approach is very sensitive to detecting the substances in human plasma. The technique might be used to analyse the medications mentioned in bioequivalence studies and therapeutic drug monitoring (23).

- **Kelani et al** (2015) developed spectrophotometric and chemometric methods for simultaneous determination of two anti-hypertensive drugs in their combined dosage form. In this work, spectrophotometric and chemometric techniques were used to determine the concentrations of the drugs hydrochlorothiazide (HCT) and moexipril hydrochloride (MOX). For the simultaneous determination of (MOX) and (HCT) in their bulk powder and medicinal dosage form, five distinct precise, sensitive, and reproducible techniques were used. The new absorbance subtraction (AS) approach is the first technique. The new amplitude modulation

(AM) technique is the second technique. The third approach uses the newly developed extended ratio subtraction (ERS) method in conjunction with the ratio subtraction (RS) approach. Principal Component Regression (PCR) and Partial Least Squares (PLS) are two of the multivariate calibration techniques used in the fourth and fifth approaches, respectively. The suggested methods were tested with lab-prepared mixes and effectively used for the analysis of their medicinal formulations. By using the common addition approach, the proposed methods' validity was further evaluated. The outcomes of using the suggested techniques were statistically examined and contrasted with those of a previously described technique (24).

- **Atole et al** (2018) demonstrated the ultraviolet spectroscopy and its pharmaceutical applications. Due to the rising demand for samples of complex matrixes, biotherapeutic products, and multicomponent formulations, quick and simple analytical procedures are required. Numerous UV spectrophotometric techniques were employed for these purposes. Numerous UV spectrometric techniques have been developed using the additivity principle, absorbance contrast, and processing of absorption spectra. Information on the simultaneous equation method, difference spectrophotometry, derivative spectrophotometry, absorbance ratio spectra, derivative ratio spectra, successive ratio - derivative spectra, Q-absorbance ratio method, absorptivity factor method, dual wavelength method, absorption factor method, multivariate chemometric methods, and isosbestic point method is presented in this review (25).

- **Ping et al** (2006) demonstrated the synergism of hydrochlorothiazide and nitrendipine on the reduction of blood pressure variability in spontaneously hypertensive rats. Seventy animals were randomly divided into seven groups. The doses were 5 and 10 mg/kg for nitrendipine, 10 and 20 mg/kg for hydrochlorothiazide and 10+5, 20+10mg/kg, respectively, for the combination of these two drugs and 0.8% carboxym-ethylcellulose as control. The drugs were given via a catheter of gastric fistula. BP was then continuously recorded for 5 h from 1 h before drug administration to the end of 4th hour after drug administration, in conscious and freely moving rats. The effects on both BP and BPV reduction of the combination of hydrochlorothiazide and nitrendipine were greater than the single drug in SHR. The two drugs possessed an obvious synergism on both systolic blood pressure (q=1.79 with small dose and q=1.23 with large dose) and systolic blood pressure variability reduction (q=1.79 with small dose and q=1.39 with large dose) in SHR. The present work clearly

demonstrated that there was a synergistic effect between hydrochlorothiazide and nitrendipine in lowering and stabilizing BP in SHR (26).

IV. CONCLUSION

In this review article various published analytical methods for the simultaneous estimation of nitrendipine and hydrochlorothiazide along with various other drugs were reported. These methods are valid, accurate, precise, reliable and reproducible as per validation parameters. Accuracy of the method was studied by recovery experiments. The recovery was performed at three levels, 80, 100 and 120% of both drug nitrendipine and hydrochlorothiazide. New analytical method could be developed from these methods by changing the chromatographic conditions.

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