A REVIEW ON THE DEVELOPMENT OF ANALYTICAL METHODS BY RP HPLC FOR SACUBITRIL/ VALSARTAN

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ABSTRACT

Cardiovascular breakdown is one among the main sources of morbidity and mortality around the world. FDA has approved Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, for the treatment of Heart failure. Sacubitril/valsartan will probably be a promising anti-Heart failure drug within the near future. This Review centers around the Recent Developments in Analytical Techniques and optimization methods for Estimation of Valsartan and Sacubitril. Sacubitril (neprilysin inhibitor) and valsartan (angiotensin receptor blocker) is a custom medication used to diminish the gamble of death and hospitalization in individuals with specific sorts of trademark long-proceeding (constant) coronary disappointment. Comparing Entresto's effectiveness and safety to Valsartan's effects on cognitive function in patients with chronic heart failure and preserved ejection fraction Future research should reveal the findings of a fraction multicenter, randomised, double-blinded experiment that is evaluating the safety and long-term neurocognitive effects of sacubitril/valsartan. From the Reviewed Literature clearly HPLC is an overall accessible means of testing in Pharmaceutical Laboratory.

Keywords: RP HPLC, Sacubitril/valsartan, coronary failure, angiotensin receptor-neprilysin inhibitor Analytical methods.

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INTRODUCTION

Sacubitril/valsartan is the first agent to be approved in a new class of drugs called angiotensin receptor neprilysin inhibitor (ARNI). THE COMBINATION IS SOLD UNDER THE BRAND NAME "ENTRESTO" BY NOVARTIS AND HAS BEEN APPROVED IN MORE THAN 57 COUNTRIES, INCLUDING INDIA[(1)]. Current US and European treatment guidelines recommend neprilysin inhibitor and angiotensin receptor blocker. Combination as a first line treatment for patients who suffer from chronic heart failure as a result of hypertension with a lower-than-normal ejection fraction[(2)]. Sacubitril/valsartan was also more effective than enalapril in slowing disease progression, by

decreasing the risk of worsening HF requiring hospitalization or emergency admission and the need for intensification of therapy, HF devices or cardiac transplantation. Overall, the results indicate that sacubitril/valsartan should be started in the earliest symptomatic stages of the disease. An analytical method dedicated to the analysis of a drug compound in a given matrix should be developed in a critical manner; presented review is focused on the use of different analytical method like HPLC (High Performance Liquid Chromatography)[3].

Valsartan occurs as a white powder. It is very soluble in methanol and ethanol (99.5 %) and practically insoluble in water. It has molecular formula $C_{24}H_{29}N_5O_3$; weight formula 435.52, and chemical name (2S)-3-Methyl-2-(N-{[2'-(1H-tetrazole-5-yl) biphenyl-4-yl] methyl} pentan-amido) butanoic acid. Pka and Log P Acid (pKa=4.73)

Carboxylic (pKa=3.9) Log P: 1.499

Sacubitril occurs as a white powder consisting of thin hexagonal plates. It is freely soluble in water. It has molecular formula $C_{24}H_{29}NO_5$. Weight formula 411.49 g/mol and chemical name 4-[[(2S, 4R)-5-ethoxy-4-methyl-5-oxo-1-(4-phenylphenyl) pentan-2-yl] amino]-4-

Oxo butanoic acid Pka and Log P Acid (pKa=4.6) Log P: 1.29[4,5]

New FDA-approved medication Entresto® (sacubitril/valsartan) is used to treat heart failure. It includes valsartan (VAL) **Figure 1**, an angiotensin II Type-1 receptor blocker, and sacubitril (SAC) **Figure 2**, a prodrug that inhibits neprilysin[6].

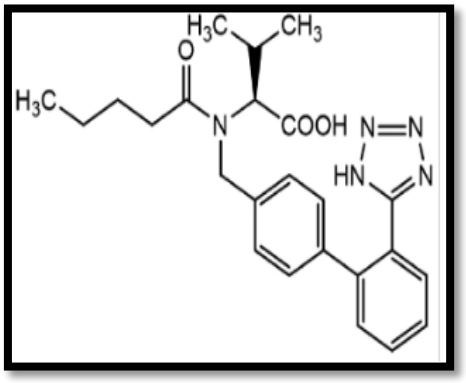

Figure 1 Structural formula of valsartan

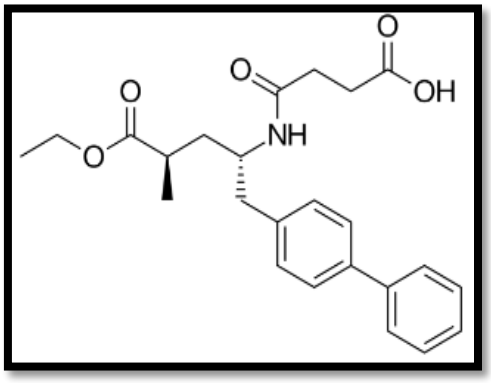

Figure 2 Structural formula of sacubitril

The pharmacological action of this medication is comparable to that of ACE inhibitors (angiotensin-converting enzyme), which dilate the veins and arterioles and suppress aldosterone production, lowering blood pressure and reducing water and salt retention. In Indonesia, angiotensin II type 1 receptor antagonists are commonly used to treat a variety of conditions, including hypertension, heart failure, myocardial infarction, and diabetic nephropathy.

Numerous analytical techniques have been created over time[7].

Co Diovan, Valesco, Diovan, Valsartan Ni, and Exforge are among the trade names currently in use in Indonesia.

There have been a number of methods published for analyzing valsartan/sacubitril in both pure chemicals and pharmaceutical formulations as well as biological fluids[8].

For quantitative valsartan/sacubitril level determination, a wide variety of analytical techniques has been created to date.

Comparing Entresto's effectiveness and safety to Valsartan's effects on cognitive function in patients with chronic heart failure and preserved ejection fraction Fraction to assess the long-term neurocognitive safety of neprilysin inhibition by sacubitril[9].

PHARMACOLOGY

Mechanism of Action

As an angiotensin receptor neprilysin inhibitor (ARNI), Entresto works by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan.

The simultaneous augmentation by LBQ657 of peptides that are destroyed by neprilysin, such as natriuretic peptides (NP), and inhibition by valsartan of the harmful effects of angiotensin II are responsible for the complementary cardiovascular benefits and renal effects of Entresto in heart failure patients.

CGMP concentrations rise because of NP activation of membrane-bound guanylyl cyclase-coupled receptors, which in turn promotes vasodilation, natriuresis and diuresis, increased glomerular filtration rate, and renal blood flow.[10]

Table 1Valsartan dosages in other commercially available products as well as the dosages of sacubitril and valsartan in Entresto

Entresto dose	dosage of Sacubitril compared to the advised Entresto dosage	Valsartan dosage in comparison to the advised Entresto dosage	The dose of valsartan in various commercially available formulations delivers the same valsartan exposure (AUC) as the advised Entresto dose.
24mg/ 26 mg	24 mg	26 mg	40 mg
49mg/ 51 mg	49 mg	51 mg	80 mg
97mg/ 103 mg	97 mg	103 mg	160 mg

ANALYTICAL METHODS

The major goal of developing and validating analytical methods is to demonstrate that they are accurate, specific, exact, and robust for the given substance. Analytical technique validation criteria in accordance with ICH and USP.

Various analytical techniques have been established to determine the dosage of valsartan and sacubitril in tablet, liquid, and bulk forms, according to literature review[11].

The significance of developing methods in combination

The main goal of scientific methods is to collect data on productivity (which may be directly related to the need for a specific dose), impurity (related to medication safety), bioavailability (drug uniformity and release), stability (shows the degradation product), and effect of producing factors to ensure that the drug product's assembly is consistent. By using RP-HPLC, many anti-hypertensive drugs and their combination drugs are identified[12].

VALSARTAN/SACUBITRIL METHOD DEVELOPMENT AND VALIDATION AND OPTIMIZATION

Arti M. Jadhav *et al*

Sacubitril with Valsartan tablet dosage estimation. A Grace C18 (250 mm x 4.6 ID, 5 micron particle size) column and a methanol:water ratio were used to achieve chromatographic separation. (90:10v/v) as the mobile phase, with a flow rate of 1 ml/min (millilitres per minute), and UV detection at a wavelength of 244 nm. The linearity of sacubitril and valsartan was found to be 12–60 g/ml. (R2=0.9987) and 13-65 g/ml, respectively (R2 =0.9979). At 50%, 100%, and 150%, the accuracy of the current approach was assessed. Sacubitril's recovery was observed to vary from 99.13% to 101.25%, while valsartan's recovery ranged from 98.92% to 101.80%. Studies with intermediate precision were conducted, and the RSD values were under 2%. Sacubitril's LOD (0.096 g/ml) and LOQ (0.293 g/ml) and valsartan's LOD (0.280 g/ml) and LOQ (0.849

g/ml) values were lower, indicating strong sensitivity of the approach[13].

G.Sireesha *et al*

The procedure was carried out using different columns, including the C18, Hypersil, Lichosorb, and Inertsil ODS columns. As it provided good peak shape and resolution at 1.0 ml/min flow, symmetry (4.6 x 250mm, 5 m) was found to be suitable. For Saccubitril and Valsartan, the overall recovery was determined to be 100.34% and 100.22%, respectively. The created method's accuracy is well within the acceptable range, according to the validation, demonstrating the method's ability to demonstrate high accuracy and reproducibility[14].

T. Gopi Raju *et al*

Quantitative analysis of Sacubitril and Valsartan using Inertsil C18 150x4.6mm, 3.5µ column with a flow rate of 1ml/min. The buffer containing 2.5g of Hexane sulphonic acid Buffer and Acetonitrile in the ratio of 70: 30 is used as mobile phase. The detection was carried out at 224nm. The proposed method shows good linearity in the concentration range from 2.6µg/ml to 36µg/ml for Sacubitril.Valsartan concentration range from 2.6µg/ml to 39µg/ml. Precision and recovery study results are in between 98-102%. This method shows good resolution of sacubitril and valsartan[15].

T. Naga Raju *et al*

The chromatographic separation was optimized by gradient HPLC on an Inertsil ODS C18 column (250 x 4.6 mm, 5) with a mobile phase made up of a mixture of buffer (pH-2.7), acetonitrile, and methanol in the ratios of 25:60:15% v/v/v in the ratio of 30:50:20% v/v at a flow rate of 1.0mL/min with UV detection at 245nm. Valsartan and sacubitril had respective retention times of 3.407 and 4.280 minutes. In accordance with ICH criteria, the developed reversed-phase high performance liquid chromatographic (RP-HPLC) method was verified. Results showed that the suggested RP-HPLC process is effective for the intended purpose and can be quickly applied for routine quality control of valsartan and sacubitril in combined dosage forms[16].

Trefi S *et al*

Sacubitril and Valsartan Combination Quantitation by New Methods in Tablet Ion-Pair HPLC Column for Ion-Pair Method: Standard C18 45% of 10-3 M cetyltrimethylammonium bromide (Cetrimide) plus 55% ACN make up the mobile phase (PH -10) Average Recovery: 95 to 105% UV-Detector and a Shimadzu LC-20 AT with a diode array detector are the detectors. The method used for quantification of sacubitril/valsartan with related substance and impurities, degradation product with good baseline separation[17].

VALSARTAN METHOD DEVELOPMENT

Alexander S *et al*

Valsartan was identified in nanoparticles using a method developed and validated by HPLC. phenomenex C18, 250mm × 250mm, HPLC column 250 nm wavelength, 4.6 mm id Ammonium formate and acetonitrile (57:43 v/v) constitute the mobile phase. Using HPLC As a result that this technique offers accurate outcomes at a lower cost than more effective techniques
methods for detection[18].

Sacubitril QBD approach

Bommi S ***et al***

High Performance Liquid Chromatography Quantification of Related Substances and Sacubitril Degradation Products Using Quality by Design Approach. Phenyl hexyl column, QbD-assisted HPLC Mobile Phase: 10 mM KH2PO4 as a Mobile Phase-A, pH-adjusted to 2.1 Methanol: acetonitrile, 70:30 v/v In a gradient Mode, a solvent combination was used as the mobile phase-B. Detection Flow Rate: 0.8 ml/min 254 nm, the wavelength 0.9989% is the correlation coefficient. A good method operable design range for the experimental chromatographic conditions was shown by the developed method. Under acidic, basic, and oxidative stress, SBT was forced to degrade, which demonstrated that the approach is stability suggesting[19].

SUMMARY AND OUTLOOK

In summary, the active ingredient in Entresto, sacubitril, is a neprilysin inhibitor whose mechanism of action could result in unintentional increases in beta-amyloid levels in the brain. In this review, these methods are shown to be both economical and compliant with the validation conditions. These techniques can be regularly used to analyse this combination in future developments [20-22]. Because of the synergistic effect on lowering blood pressure and reduction of side effects of one drug by another. Side effects of the individual drugs can be mitigated by using a complementary agent rather than than increasing the dose of a single agent [23-24]. Instead of increasing the dosage of a single agent, side effects of the individual drugs can be reduced by utilising a complementary agent. As a result, the recommended review analytical methods can be utilised for routine analysis of sacubitril and valsartan in bulk and pharmaceutical dose form [25].

CONCLUSION:

As there is no approved method for valsartan/sacubitril in bulk and in commercially available tablets with less retention time, accuracy, and sensitivity in the Indian Pharmacopeia, British Pharmacopeia, and United States of Pharmacopeia. In order to reach these goals, very sensitive and precise methods of analysis are required. The improvement of life quality has inspired significant research in drug design, bioavailability, and safety. It is important to create an analytical technique specifically for analysing a pharmacological molecule in a given matrix. The regular analysis of sacubitril and valsartan in bulk and pharmaceutical dose form can therefore be performed using a novel approach by using different buffer and concentrations that can be developed in future research, validated, and compared with the present method.

This review's statistical examination of the development and validation process's successful outcomes shows promising findings.

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