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Simultaneous Estimation of Sacubitril and Valsartan Combination of Drug in Tablet Dosage Form Using Hydrotropy by UV Spectrophotometry

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Review Article

Abstract

Sacubitril is a neprilysin inhibitor (A prodrug) and is used in combination with valsartan to reduce the risk of cardiovascular events in patients with chronic heart failure. It is antihypertensive drug. Valsartan is an Angiotensin Receptor Blocker (ARB) that may be used to treat a variety of cardiac conditions including hypertension, diabetic nephropathy and heart failure. The reviewed highlights various analytical techniques such as high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), UV Spectroscopy, high performance thin layer chromatography (HPTLC), liquid chromatography coupled to tandem mass spectrometry (LC-MS), RP-HPLC and other chromatographic method used. The combination of these drugs with different method was examine and the commonly use of the drugs in hypertensive.

Keywords: Sacubitril, Valsartan, Drug profiling, HPLC, HPTLC.

1. Introduction

Analytical chemistry is a branch of science which is useful in various fields of science in pharmaceuticals and medicine due to its versatile application. It deals with two aspects of chemical analysis i.e. qualitative and quantitative analysis. The qualitative analysis reveals the chemical identity of the sample and the other quantitative analysis gives the amount of one or more components present in numerical terms (1). Spectroscopy is the study of interaction of electromagnetic radiation with matter. There are present Spectrophotometric assay of drugs rarely involves the measurement of absorbance of samples and these containing only one absorbing component. If the chemical formula of the samples is known, the identity and concentration of the interferents are known and the extent of interference in the assay may be determined. It is based on the principle of spectroscopy is the measurement of spectrum of a sample containing atoms or molecules. There is the graph of intensity of absorbed or emitted radiation by sample verses frequency (ν) or wavelength (λ) and

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Spectrometer is an instrument design to measure the spectrum of a compound (2). It has important part of Spectrophotometric Methods of Simultaneous estimation of Analysis for Drugs in Combination is generally done by some separation techniques using chromatographic methods like HPLC, GC and HPTLC etc. These methods are accurate and precise with good reproducibility, but these are costly for analysis. Simultaneous estimation is simpler and cost-effective method for Spectrophotometric analysis fulfils such requirement where the simultaneous estimation of the drug combination can be done with similar effectiveness as that of chromatographic methods. There are different spectrophotometric methods are available which can be used for the analysis of a combination of drug samples (3).

Spectrophotometric method

It is the bough of science commerce with the study of interaction between electromagnetic radiation and matter. It is a most powerful device available for the study of atomic and molecular structures and is used in the analysis of wide range of samples. Some of the commonly used Spectrophotometric methods are as follows,

1. Simultaneous equation method (Vierdott's method)
2. Derivative Spectrophotometric method
3. Absorbance ratio method (Q-Absorbance method)
4. Solvent extraction method
5. Dual wavelength method
6. Geometric correction method
7. Orthogonal poly nominal method
8. H-point standard addition method
9. Least square approximation method

1.1 Simultaneous equation method

If a sample contain two absorbing drugs (X & Y) each of this absorbs at the λ_{max} of each other i.e. λ_1 and λ_2, it may be possible to determine both the drugs by the technique of simultaneous equation method provided that certain criteria apply.

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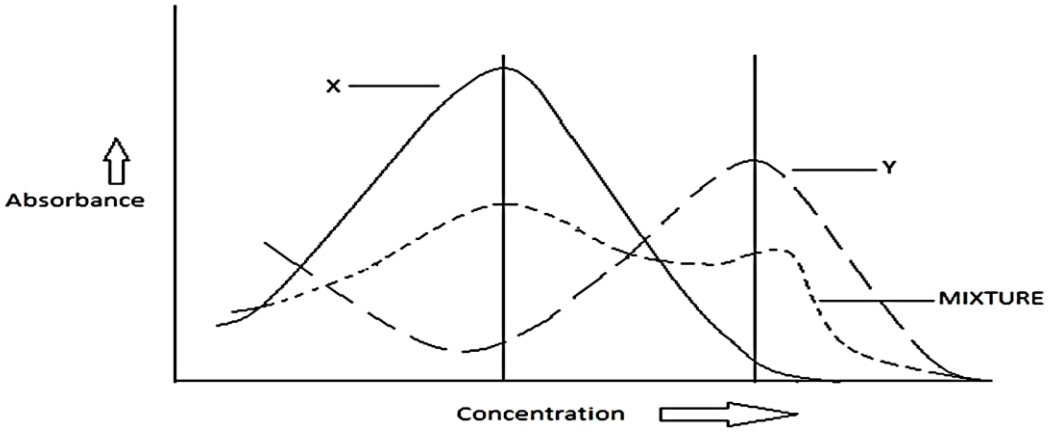

Figure 1: Overtone spectra of substance X and Y

- The information required is:
- The absorptivity of X at λ_1 and λ_2 and ax_1 and ax_2 respectively.
- The absorptivity of Y at λ_1 and λ_2 and ay_1 and ay_2 respectively.
- The absorbance of the diluted sample at λ_1 and λ_2, A_1 and A_2 respectively.
- Let C_x & C_y be the concentration of X & Y respectively in the diluted sample. Two equations are constructed based upon the fact that at λ_1 and λ_2 the absorbance of the mixture is the sum of the individual absorbance of X & Y.

At $$\lambda_1, \quad A_1 = ax_1bcx + ay_1bcy \tag{1}$$

At $$\lambda_2, \quad A_2 = ax_1bcx + ay_2bcy \tag{2}$$

On rearranging equation (2)

$$C_Y = \frac{A_2 - ax_2C_x}{ay_2} \tag{3}$$

Substitution C_Y in equation (1) and rearranging, gives:

$$C_x = \frac{A_2ay_1 - A_1ay_2}{ax_2ay_1 - ax_1ay_2} \tag{4}$$

And $$C_y = \frac{A_1ax_2 - A_2ax_1}{ax_2ay_1 - ax_1ay_2} \tag{5}$$

The ratios are:

$$\frac{A_2/A_1}{ax_2/ax_1} \text{ and } \frac{ay_2/ay_1}{A_2/A_1}$$

there is using two equations the concentration of component X and component Y in the mixture of sample which can be determined.

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1.2 Derivative Spectrophotometry

Derivative spectrophotometry involves the transformation of absorption spectra (zero-order) into first-, second- or higher order derivative spectra. A first order-derivative spectrum is a plot of the rate of change of the absorbance(dA) against wavelength (dλ).

A second order-derivative spectrum is a plot of the curvature of the absorption spectrum ($d^2A/d\lambda^2$) against wavelength

$$\frac{d^2A}{d\lambda^2} = d^2A \times \frac{Cd}{d\lambda^2}$$

d^2A = (1%, 1 cm)

Where,

A = the absorbance at wavelength λ

c = the concentration of the absorbing solute

d = the thickness of the absorbing layer in cm (cuvette)

In solvent extraction method quantitation of individual drugs in combinations has been performed by separation of individual drugs based on their selective solubility followed by spectrophotometric measurement. If the interference from the other absorbing substances is large, it may be possible to separate the absorbing interferent from the analyte by solvent extraction procedure. These are particularly appropriate for acidic or basic drugs whose state of ionization determines their solvent partitioning behaviour. The judicious choice of pH of the aqueous medium may affect the complete separation of the interferents from the analyte, the concentration of which may be obtained by a simple measurement of absorbance of the extract containing the analyte (4).

2. Hydrotropy Theory

Hydrotropy is the term discovered by 'Carl A. Neuberg' in 1916. Now days the hydrotropic solution possess high industrial demand due to their exclusive features like better solubility, absence of fire hazards, good recovery and fast separation feature without any emulsification problem. It produces eco-friendly nature and effective water solubility. It involves the water-soluble or water-insoluble categories. Most of the newly developed drug molecules are lipophilic in nature and pitiable solubility is the most difficult problems of these drugs. Drug analysis in final product is important step. There are available some organic solvents such as methanol, chloroform, dimethylformamide and acetonitrile have been employed for solubilization of poorly water-soluble drugs to carry out analysis of poorly water-soluble drugs Hydrotropic solubilization is based on analytical method (5). The process is mainly related to quantitative term which is defined as the concentration of the solute in a saturated solution at a certain temperature, and in qualitative terms is defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. The solubility of the drug may be expressed as parts, percentage, molarity, molality, volume fraction and mole fraction.

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Table 1: Expression for approximate solubility

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

Hydrotropy solubilisation is process of addition of a large amount of the second solute results which increase in the aqueous solubility of another solute. There are generally consist of two hydrotropic salts known as, anionic part and hydrotropic aromatic ring. It contains the ionic organic salts, which increase the solubility in the solvent are "salt in" and those salts which decrease solubility are "salt out" solute.

Many solvents have large anion and cation which is completely solubilize in water called Hydrotropic salts.

This phenomenon known as "hydrotropism". It does not show colloidal properties (6).

Characteristics of Hydrotropes-

1. Completely soluble in water and practically insoluble in the system.
2. Hydrotropes are surface active and aggregate in aqueous solution because of their amphiphilic structure.
3. Should not produce any temperature when dissolved in water.
4. Cheap and easy availability.
5. Nontoxic and non-reactive.
6. Insensitive to temperature effects, when dissolved in water.
7. The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other unique advantages of the hydrotrope.

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Advantages of Hydrotropic Solubilization

1. Hydrotropy is suggested to be superior to other solubilization methods, such immiscibility, micellar solubilization, co-solvency and salting in, because the solvent characteristics are independent of pH, and have high selectivity and does not require emulsification.
2. It only requires mixing the drug with the hydrotrope in water.
3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system (7).

3. Drug Profile

Pharmaceutical analysis is essential part of pharmaceuticals means is a medical drug. These explain for a pharmaceutical is active pharmaceutical ingredient (API) to distinguish it from a formulated product or drug product is prepared by formulating a drug substance with inert ingredient (excipient) to prepare a drug product that is suitable for administration to patients. pharmaceutical analysts play a major role in estimation of any drug for the identity, safety, efficacy, and quality of drug product and their safety and efficacy studies required that drug substance and drug product meet two critical requirements.

1. Established identity and purity.
2. Established bio availability/dissolution.

These are necessary part of the simultaneous estimation of any drug (8).

The main plan of the present study was to develop accurate, precise and selective reverse phase HPLC assay procedure for the analysis of Sacubitril and Valsartan in tablet dosage form. The estimation of planned method is done according to the ICH guidelines. There was found many methods to the survey of different literature are available for determination of Valsartan individually and also many other methods used in combination with other drugs (9).

There are widely used analytical tool in the pharmaceutical industry. The drug development processes many types of chromatographic methods are used to determine the quality of the drug substance (active pharmaceutical ingredient) and drug product. It has involved the, Liquid chromatography, reversed phase high performance liquid chromatography (RP-HPLC) method with UV detector, reversed phase ultraperformance liquid chromatography (RP-UPLC), high performance thin layer chromatography (HPTLC). HPLC method has been reported for simultaneous determination of Sacubitril and Valsartan in combination.

In the proposed study an attempt will be made to develop a HPLC method for simultaneous estimation of Sacubitril and Valsartan (9). This new drug was discovered and developed as tablet dosage form called ENTRESTO by Novartis, which was then approved by US Food and Drug Administration (FDA) in July 2015 for the treatment of heart failure. ENTRESTO is a combined dosage form which contain sacubitril (SAC), a prodrug that results in neprilysin inhibition and

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valsartan (VAL) which is angiotensin II Type-1 receptor blocker), is the first medicine in this category. This combined drug (previously known as LCZ696) is also a useful antihypertensive drug (10). Sacubitril or Valsartan is a first-in-class angiotensin receptor- neprilysin inhibitor (ARNi) approved for the treatment of HF.

3.1 Valsartan

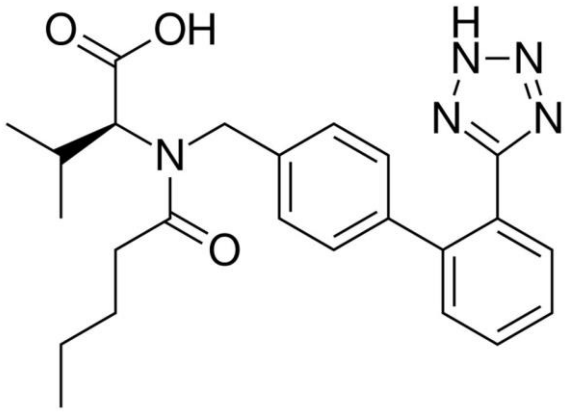

Figure 2: Chemical structure of valsartan

Valsartan is a tetrazole derivative; (2S)-3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] amino] butanoic acid with molecular formula C24H29N5O3...chemical structure is shown in figure.

History of Valsartan- VAL was first developed by Novartis and was sold under the brand name DIOVAN. It is also available in combination with other antihypertensive drugs.

Physiological properties of valsartan: Valsartan is a white coloured powder that is freely soluble in ethanol, methanol and acetonitrile and sparingly soluble in water. Valsartan appears in the melting range of 105-110˚C and the specific rotation [α] D/20 in methanol being 68˚. The partition coefficient of Valsartan is 0.033 (log P=1.499), suggesting that the compound is hydrophilic at physiological pH. The compound is stable under storage in dry conditions VAL is soluble in the neutral pH range (11).

Mechanism of action

Sacubitril (AHU-377), neprilysin inhibitor, is a prodrug that is activated to the active metabolite 'Sacubitrilat' (LBQ657) by de-ethylation via esterases. Sacubitril, thus, increases the levels of these peptides, promoting natriuresis, vasodilation and reduction of ECF volume via sodium excretion; eventually reducing preload and ventricular remodelling in summary, the CV and renal benefits of sacubitril/valsartan in HF patients are attributed to the increased levels of peptides that are degraded by neprilysin and the simultaneous inhibition of the effects of AT1 receptor by valsartan.

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3.2 Sacubitril

Sacubitril is chemically designated as 4-{[(2S,4R)-1-(4-Biphenylyl)-5-ethoxy-4-methyl-5oxo-2-pentanyl]amino}-4-oxobutanoic acid. Its molecular formula is C24H29NO5, and its molecular weight is 411.49 g/mol (11).

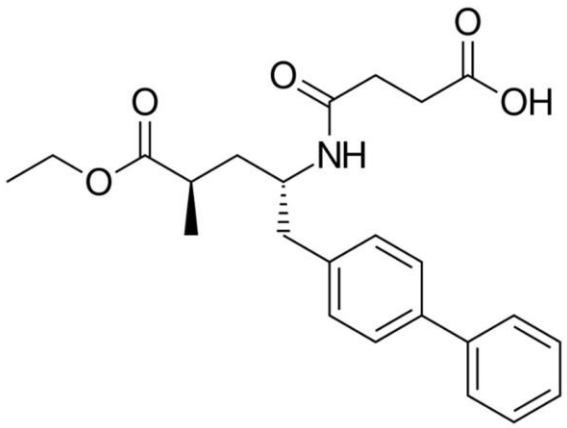

Figure 3: Chemical Structure of Sacubitril

Sacubitril is a neprilysin inhibitor and is used in combination with valsartan to reduce the risk of cardiovascular events in patients with chronic heart failure (NYHA Class II-IV). The combination drug, sacubitril/valsartan is used in place of an ACE inhibitor or ARB. It was approved under the FDA's priority review process for use in heart failure on July 7, 2015 {8}.

Mechanism of action

Sacubitril (AHU-377), neprilysin inhibitor, is a prodrug that is activated to the active metabolite 'Sacubitrilat' (LBQ657) by de-ethylation via esterases. Sacubitril, thus, increases the levels of these peptides, promoting natriuresis, vasodilation and reduction of ECF volume via sodium excretion; eventually reducing preload and ventricular re-modelling.

Physical and chemical properties of both drugs Sacubitril/Valsartan complex comprises of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. A single complex consists of 6 valsartan anions, 6 sacubitril anions, 18 sodium cations, and 15 molecules of water, resulting in the molecular formula C288H330N36Na18O48 _15H2O and a molecular mass of 5748.03 g/ mol.6,13 The substance is a white powder consisting of thin hexagonal plates. It is stable in solid form as well as in aqueous (watery) solution with a pH of 5 to 7, and a melting point of about 138˚C (280 F) (12).

The main uses of both drugs are valsartanis used in Hypertensive, diabetic nephopathy and heart failure and sacubitril is used as antihypertensive drug and it is a prodrug which used in combination with valsartan.

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4. Conclusion

Spectroscopy is one of the most widely used technique to carry out the analysis of pharmaceutical preparation. UV spectroscopy is based on the measurement of spectrum of sample contains atom. A broad range of techniques are available for the analysis of sacubitril and valsartan in pharmaceutical formulation. These techniques are very useful in the structure elucidation of organic molecule. The review would help analytical chemist in knowing the key solvent and their combination. The effective combination of parameters should be minimizing the cost of the analysis and reduce the time required for producing are liable analytical method. This method is also used as a detector for HPLC.

References

1. *Simultaneous estimation of multicomponent formulations by UV-visible spectroscopy: an overview.* **Chaudhary J, Jain A, Saini V.** 2011, International Journal of Pharmacy, pp. 81-83.

2. **Boylan JC, Swarbrick J.** Encyclopedia of pharmaceutical technology. [book auth.] Marcel Dekker. 1998, pp. 217-224.

3. **Beckette AH, Stenlake JB.** Practical Pharmaceutical Chemistry, Part I. New Delhi : CBS Publishers and Distributors, 1997.

4. **Lachman L, Herbert A, Lieberman, Kanig JL.** The theory and practice of industrial. Bombay : Varghese publishing house, 1987.

5. *Advances in hydrotropic solutions: an updated review.* **Dhapte V, Mehta P.** 2015, St. Petersburg Polytechnical University Journal: Physics and Mathematics, pp. 424-435.

6. *Hydrotropic Solubilization: Tool for Eco-Friendly Analysis.* **Ghogare D, Patil S.** 2018, International Jour of Pharmacy and Pharmaceutical Research, pp. 300-322.

7. *New spectrophotometric determination of hydrochlorothiazide in tablets using mixed hydrotropic solubilization technique.* **Maheshwari RK, Rajput MS, Sharma S, Nair V.** 2010, Der Pharmacia Lettre, pp. 70-74.

8. *New method development and validation for the simultaneous estimation of sacubitril and valsartan in a bulk and pharmaceutical dosage forms.* **Vaka S, Parthiban P.** 2017, Int J Res, pp. 17-24.

9. *Simultaneous estimation of sacubitril and valsartan in synthetic mixture by RP-HPLC method.* **Patel KH, Luhar SV, Narkhede SB.** 2016, J Pharm Sci Bioscientific Res, pp. 262-269.

10. *Application of TLC-Densitometric Method for Simultaneous Determination of Sacubitril and Valsartan in their Newly Approved Pharmaceutical Formulation.* **Attia KA, Nassar MW, El-Olemy A, Ramzy S.** 2018, Eurasian Journal of Analytical Chemistry, pp. 67-75.

11. *ANALYTICAL METHODOLOGIES FOR DETERMINATION OF VALSARTAN: AN OVERVIEW.* **Sivakamasundari G, Kannappan N.** 2017, World Journal of Pharmacy and Pharmaceutical Sciences, pp. 605-617.

12. *Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor.* **Dargad RR, Prajapati MR, Dargad RR, Parekh JD.** 2018, Indian heart journal, pp. 102-110.

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A Brief Author Biography

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