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REVIEW ARTICLE

MODERN ANALYTICAL TECHNIQUES FOR VALACYCLOVIR HYDROCHLORIDE: AN OVERVIEW

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ABSTRACT

Valacyclovir the L-valyl ester of acyclovir is an oral prodrug. It is guanine nucleoside antiviral used to treat herpes exacerbations.The current study primarily focusses on development of analytical and bioanalytical methods, along with several techniques established for the estimation of quetiapine fumarate, whether in bulk or pharmaceutical dose form. Although they enable us to use cutting-edge analytical equipment to acquire both qualitative and quantitative results, analytical methods are essential for determining compositions. The analytical method for quetiapine fumarate may be chromatographic, spectral or hyphenated. Understanding important process factors and reducing their impact on accuracy and precision are made easier with the help of these techniques. Development of analytical methods is necessary to maintain high standards for commercial product quality and to comply with legal obligations. The development of analytical techniques is essential to sustaining regulatory requirements and maintaining high standards for the quality of commercial products. Bioanalytical techniques are intended to quantify the concentration of drugs, metabolite, or usual biomarker present in different biological fluids, such as tissue extracts, urine, serum, and saliva.

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INTRODUCTION

Valacyclovir (VAC) is a nucleoside analogue DNA polymerase inhibitor. The IUPAC name of VAC is 2- (2-amino-1, 6-dihydro-6-oxo-9H-purin-9-yl-methoxy) ethyl valinate hydrochloride(Fig. 1), is the L-valine ester of ACV(1).The antiviral medication, commonly referred to as Valtrex, has been used for over 20 years to manage and treat infections caused by the vericellazoster virus as well as the herpes simplex virus types 1 and 2 (HSV-1). GlaxoSmithKline began marketing it after the FDA gave it its initial approval in 1995. (2,3).It was developed to improve ACV's oral bioavailability. Acyclovir inhibits herpes virus DNA replication in a very selective manner by enhancing absorption in virus-infected cells and phosphorylating it by viral thymidine kinase. Acyclovir triphosphate's substrate selectivity for viral DNA polymerase rather than cellular DNA polymerase enhances to the drug's specificity(4).Further applications in dermatology, such as recurrent erythema multiforme that is not responsive to ACV and is assumed or shown to be caused by HSV. Other subtypes of HSV infections include prophylaxis against orofacial herpes prior to laser cutaneous resurfacing, prophylaxis of cytomegalovirus infection in solid organ or bone marrow transplantation, primary herpetic gingivostomatitis, recurrent herpes labialis, herpes gladiatorum, eczema herpeticum, herpetic whitlow, and herpetic keratoconjunctivitis (5).

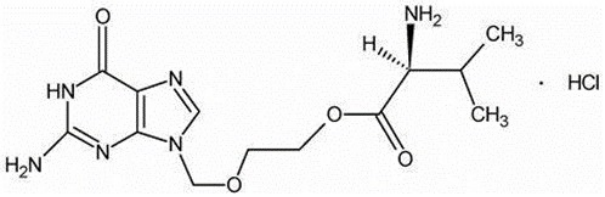

Fig. 1. Structure of Valacyclovir Hydrochloride

Need of Analytical method: Official test methods are the end product of analytical technique development. As a result, quality control laboratories used these techniques to examine the performance, identification, purity, safety, and efficacy of drug items. Analytical techniques used in production are of the utmost relevance to regulatory bodies. The applicant must demonstrate control of the entire drug development process using approved analytical methods in order for regulatory authorities to approve the medicine (6). Stability testing (Q1), validation of analytical techniques (Q2), impurities in drug substances and products (Q3), and specifications for new drug substances and products (Q6) are analytical guideline documents that the ICH recently issued (7).

Analytical Method Development by UV Spectrophotometer: The study of interactions between matter and electromagnetic radiation in the ultraviolet-visible region

Table no 1. Analytical method development using UV spectrophotometer

S. No.	Sample / Dosage form	Method / Instrument model	Solvent / Solution	Wavelength (nm)	References
1.	Bulk and tablet	Labindia UV 3000+ and Elico SL 210 (Andhra Pradesh, India) double beam UV visible spectrophotometers	0.1M HCL	237.52	10
2.	Tablet	PerkinElmer Lambda-35 UV-Visible double beam spectrophotometer	0.1N HCl	255	11
3.	Bulk drug and tablet	Double-beam Shimadzu 1700 UV spectrophotometer	0.1M HCL	508	12
4.	Tablet	UV-VIS spectrophotometer	Method A in Sodium Acetate Method B Phosphate buffer pH 5.0 Method C phosphate buffer pH 7 Method D borate buffer pH 9.0 Method E 0.1N NaOH	251,251,252,253 and 265	13
5.	Pure and tablet	UV-visible spectrophotometer	0.1M HCL	520	14
6.	Bulk drug and tablet	Shimadzu model 1700 double beam UV-Visible spectrophotometer	Method A vanillin and nitric acid Method B ethanolic PDAB and nitric acid	428 and 388	15
7.	Bulk and tablet	Shimazu-1700 Double beam UV-Visible Spectrophotometer	Distilled water	252	16

Table no 3. Analytical method development using HPLC method

S.No.	Sample	Stationary phase/column	Mobile phase	Wavelength (nm)	Flow rate (ml/min)	RT (min)	Reference
1.	Tablet	Hypersil BDS C18 (150mm x 4.6mm, 5µm particle size)	Mobile Phase-A: pH 3.5 buffer. Mobile Phase-B: Mixture of Acetonitrile and Methanol 60:40(%v/v)	254	1.5	5.86	20
2.	Tablet	150 x 4.0mm (i.d.), Stainless steel, packed with 5µm Daicel Chiral Phase Crownpack CR (+)	0.1% aqueous Phosphoric acid (85%): Methanol (90:10 V/V) as a mobile phase	254	-	-	21
3.	Tablet	ODS column	0.015 M acetic acid and methanol (95:5 v/v)	254	1.1	3.0	22
4.	Tablet	cyno column (250 x 4.6mm, 5µ)	0.1% Ammonium acetate in water) and Acetonitrile in the ration 95:5	254	-	-	23
5.	Bulk drug	Chiralpak AD (250 mm × 4.6 mm, 10µm)	n-hexane: ethanol: dimethylamine (30:70:0.1, v/v/v).	254	1.2	8.1	24
6.	Tablet	C18- column	Methanol, acetonitrile and water mixture in the ratio of 35:41.5:23.5v/v	222	1.3	2.61	25
7.	Tablet	ODS C18 column	Acetic acid in water (1: 1000): methanol (70: 30)	254	1.0	9	26
8.	Tablet	Crown Pak (150 mm x 4.6 mm), 5µ	Buffer solution: Methanol (85:15)	254	1.0	-	27
9.	Bulk drug and tablet	C8 column	Acetonitrile: Phosphate buffer pH 3 (25 mM) in the ratio of 10:90 v/v	254	1.0	-	28
10.	Bulk drug and tablet	C18 column 150×4.6mm	Methanol: Water (70:30)	252	0.8	2.2	29
11.	Bulk drug and tablet	C8 agilentzorbax column 150cm x 4.6mm x 5micron	Phosphate buffer at pH 3.0: water: methanol (50:50 % v/v)	253	1	2.02	30
12.	Tablet	Nucleosil CN column	Phosphate buffer (pH = 7) and methanol 85:15 (v/v)	254	-	6 ± 0.15	31
13.	Tablet	Hypersil ODS C-18 (250 x 4.6 mm, packed with 5 micron)	Acetonitrile: phosphate buffer (pH- 3.6) (50:50%v/v)	252	0.8	2.850	32
14.	Bulk and tablet	C18 column (Develosil) of 250×4.6mm dimensions and 5 µm	0.1% v/v Formic acid: Acetonitrile (90:10 v/v)	252	-	3.98	33
15.	Bulk and tablet	ODS C18 (250×4.6 mm i.d., packed with 5 µ particle size)	Acetonitrile: phosphate buffer (pH-3.6) in the ratio of 50:50 (%v/v)	252	0.8	2.850	34
16.	Tablet	C18 Column (250 mm × 4.6 mm, 5 µm particle size)	Methanol: Citric Acid buffer in a ratio of 60: 40 v/v	254	1	2.2 ± 0.1	35
17.	Tablet	ODS C-18 (250 x 4.6 mm, packed with 5 micron)	Acetonitrile: Phosphate buffer (pH- 3.6) (50:50%v/v)	252	0.8	2.842	36

Table no 4. Major Differences between TLC & HPTLC

Parameters	TLC	HPTLC
Technique	Manual	Instrumental
Efficiency	Less	High
Layer	Lab made	Precoated
Mean particle size	10-12 µm	5-6 µm
Layer thickness	250 µm	100µm
Plate height	30 µm	12 µm
Solid support	Silica gel, Alumina, Kieselguhr	Silica gel-Normal Phase C8 and C18-reverse phase
Spotting of sample	Manual (Capillary/Pipette)	Syringe
Volume of sample	1-5µL	0.1-0.5 µL
Separation	10-15 cm	3-5 cm
Separation time	20-200 min	3-20 min
Analysis time	Slower	Storage migration distance and the analysis time is greatly reduced
Scanning	Not possible	Use of UV/visible/fluorescence scanner

Table no 5. Analytical Method Development Using HPTLC Method

S.No.	Sample	Stationary Phase/ Column	Mobile phase	Wavelength (nm)	Reference
1.	Tablet	Silica gel 60 F_{254}	Chloroform: methanol: ammonia (50:14:2 v/v/v)	253	39

Table no 6. Bioanalytical Method Development Using Various Method

S.No.	Method	Sample/ dosage form	Stationary phase/column	Mobile phase	Wavelength (nm)	Flow rate min/ ml	Retention time (min)	Reference
1.	spectrofluorimetric	Tablets spiked plasma	-	Borate buffer solution of pH 9.0	390	-	-	42
2.	HPLC	Human plasma	Hypersil ODS C18 (150mm ×4.6mm,5.0µm)	Acetonitrile-water (85:15 v/v)	265	0.2-1.2	4.19	43
3.	HPLC-MS	Human plasma	Lichrosphere RP Select B (125 × 4.6 mm, 5 µm)	Methanol:1 mM ammonium acetate buffer (pH 6.2; 70: 30 v/v),	-	0.8	4	44
4.	RP-LC	Human Plasma	BDS Hypersil C8 column	0.01 M KH2PO4 (pH 4): acetonitrile (98.5:1.5 v/v)	245	1 -1.5	8	45
5.	RRLC	Human Plasma	Zorbax SB phenyl column	0.01M n-tetrabutyl ammonium hydrogen sulphate and methanol in the ratio of (95:5, v/v)	254	0.3	1.8	46
6.	LC–ESI/MS	Human Plasma	Graphitized carbon analytical column (2.1 mm × 125.0 mm i.d., particle size 5 µm)	Acetonitrile/water with 0.05% (v/v) diethylamine (50:50, v/v)	-	0.15	-	47
7.	LC–MS–MS	Human Plasma	C18 column	0.1% formic acid: methanol (30:70% v/v).	-	-	2.40	48
8.	LC–MS/MS	Human Plasma	Zorbax, SB C18, 4.6 × 75 mm, 3.5 µm column	10 mM ammonium formate buffer (pH 5) and methanol (80:20 v/v)	-	0.25	4.4 ± 0.2	49
9.	LC–MS/MS	Human Plasma	Inertsil CN-3 (5 µm) column	1 mM ammonium acetate buffer - methanol, 50:50 v/v	-	0.8	-	50
10.	RP-HPLC	Tablets and Human Serum	Spherisorb C18 column	Acetonitrile: methanol: 0.067 M KH2PO4 (27: 20: 53, v/v/v) adjusted to pH 6.5 with 3 M NaOH	244	-	5.13	51
11.	LC-MS/MS	Mouse and human plasma	T3 C18 column (5um, 150 × 2.1 mm	Water containing 2 mM ammonium acetate and 0.2% formic acid (v/v) (phase A) and acetonitrile containing 0.2% formic acid (v/v) (phase B)	-	0.2	-	52
12.	LC–ESI-MS/MS	Human plasma	Gemini C18 analytical column	0.1% formic acid and methanol (30:70 v/v)	-	0.8	-	53

is known as ultraviolet-visible spectroscopy. The range of wavelengths in the ultraviolet (UV) is 200–400 nm (8). The Beer-Lambert law, which it is founded on, stipulates that the relationship between a solution's absorbance and path length is one of direct proportionality. As a result, it can be used to calculate the concentration of the absorber in a solution for a particular path length. It's critical to understand how quickly absorbance varies with concentration (9).

Analytical method development by HPLC: One of the most well-established analytical procedures and by far the most extensively used separation method is high performance liquid chromatography (HPLC). Over the past 40+ years, it has been utilised in labs all over the world for pharmaceutical sciences, clinical chemistry, food and environmental evaluations, synthetic chemistry, etc (17). A liquid or a solid phase might be the stationary phase in this approach. The components of a combination can be separated via HPLC using a liquid mobile phase. The phrase "high-performance liquid chromatography" (HPLC) refers to liquid chromatography in which the stationary phase is contained in a column and the liquid mobile phase is mechanically pumped through the column (18). HPLC systems' beating heart is the column. A reproducible and symmetrical peak will be produced by a good silica and bonding procedure, which is required for precise certification. C18 (USP L1), C8 (USPL8), Phenyl (USP L11), and Cyno (USP L18) are examples of commonly used RP columns (19).

Analytical Method Development Using HPTLC Method: HPTLC is a potent analytical technique that works well for both qualitative and quantitative tasks (37). Depending on the type of adsorbents employed on the plates and the development solvent system, separation may be caused by partition, adsorption, or both phenomena. Principle, theory, instrumentation, implementation, optimization, validation, automation, and qualitative and quantitative analysis are some of the several facets of HPTLC basics (38).

Bioanalytical Method Development: Bioanalysis is covering the identification and quantification of analytes in biological samples (blood, plasma, serum, saliva, urine, feces, skin, hair, organ tissue). Bioanalysis is not only measuring of small molecules such as drugs and metabolites but also to identify large molecules such as proteins and peptides. Bioanalysis is well established in pharmaceutical companies to support drug discovery and drug development. Bioanalysis has an important role to perform the toxicokinetic (TK), pharmacokinetic (PK) and pharmacodynamics (PD) studies of new drugs. Bioanalysis is also established in clinical, preclinical and forensic toxicology laboratories. Thus, bioanalysis is an important discipline in many research areas such as the development of new drugs, forensic analysis, doping control and identification of biomarkers for diagnostic of many diseases (40,41).

CONCLUSION

In this review, the various analytical and bioanalytical techniques utilized for the estimation of Valacyclovir hydrochlorideinbulk form, dosage form as well as in human plasma. The development of analytical and bioanalytical techniques such as UV spectrophotometry, HPLC, HPTLC, RP-HPLC and other techniques has been the focus of researcher. Hyphenated techniques include LC-MS/MS, HPLC-MS, LC-ESI/MS/MS etc. All of the established analytical techniques have increased levels of automation and processing of samples are very sensitive, reliable, reproducible, and precise. A literature review is conducted for collecting data on various instrumental analytical techniques. A unique analytical approach could be developed using such data.

Competing Interests: Authors report no conflict of interest concerning this review article.

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