Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 5 Issue 7 July 2021

Mini Review

Analytical Techniques for the Assay of Valganciclovir - A Review

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Received: May 22, 2021

Published: June 11, 2021

Abstract

Valganciclovir is an anti-viral drug used for the treatment of Cytomegaloviral infection in patients with HIV/AIDS and also for the treatment after the organ transplantation and it suppress the infection on long term use instead of curing the infection. In the present paper the authors have reviewed the analytical methods already published till now in the literature for the estimation of Valganciclovir in pharmaceutical formulations and in biological samples.

Keywords: Valganciclovir; Analytical Techniques

Introduction

Valganciclovir (Figure 1) is chemically 2-[(2-amino-6-oxo-6, 9-dihydro-3H-purin-9-yl) methoxy]-3-hydroxypropyl (2S)-2-amino-3-methylbutanoate derivative. It is also the L-valine ester of Ganciclovir. Due to the hydrolysis of ester linkage, Valganciclovir converts in to Ganciclovir [1]. Valganciclovir has been developed for the prophylactic action against Cytomegalo viral infection for the immuno suppressant patients with organ transplantation and also for AIDS patients [2-5]. Valganciclovir has a molecular formula $C_{14}H_{22}N_6O_5$ and molecular weight 354.362 g/mole and the pKa value is found to be 7.6. Valganciclovir is freely soluble in water and sparingly soluble in methanol. Valganciclovir shows its action by activating the viral protein kinase HCMV UL97 and there by subsequent phosphorylation by the cellular kinases. Valganciclovir is available as tablets with brand names Valgan (Cipla Ltd, India), VALCIP (Cipla Ltd, India), Cymgal (Biocon Ltd), Valgacel (Intas Biopharmaceuticals), Vegacyte (Panacea Biotec) etc. with a labelled claim 450 mg.

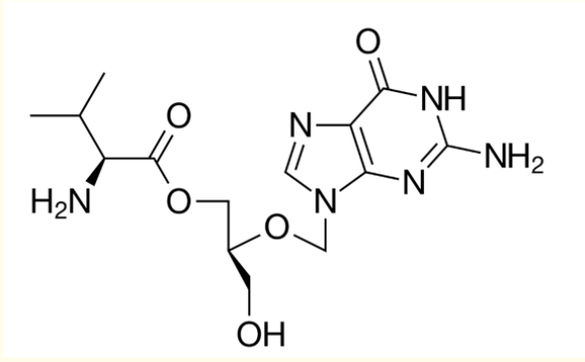

Figure 1: Chemical structure of Valganciclovir.

Discussion

Sumanta Mondal., *et al.* developed zero order and first order derivative spectrophotometric methods [6] in water, phosphate buffer pH 2.0, phosphate buffer pH 4.0 and phosphate buffer pH 5.0 reagent solutions for the determination of Valganciclovir hydrochloride and the linearity was observed 5 - 60 µg/ml in all the methods. Bahlul., *et al.* [7] and Awen., *et al.* [8] have used developed spectrophotometric technique for the determination of Valganciclovir using methanol and the λ_{max} was reported at 252 and 254 nm respectively and Beer-Lambert's law was followed over the concentration range 5-30 µg/ml. Karthik., *et al*. proposed area under curve (AUC) technique [9] for the assay of Valganciclovir in distilled water

with the wavelength selection 247 - 25 nm but very low linearity range (1 - 6 µg/ml) was reported. Abdulrahman., *et al.* established two non-aqueous titrimetric and one visible spectrophotometric method for the assay of Valganciclovir [10]. Non-aqueous titration was carried out in glacial acetic acid with acetous perchloric acid in the presence of mercuric acetate and the same was also carried out using potentiometry and the linearity was observed in the range 4 - 20 mg. The authors have also developed a visible spectrophotometric method using para dimethyl amino benzaldehyde by which an yellow chromogen was developed due to the condensation reaction with Valganciclovir. The yellow chromogen has shown the absorption maxima (λ_{max}) at 420 nm and Valganciclovir has shown linearity over the concentration range 5 - 50 µg/mL in this method.

Dogan-Topal., *et al.* developed a RP-HPLC method for the determination of Valganciclovir in human serum and tablets by using acetonitrile: methanol: KH_2PO_4 (pH 5.0) (40:20:40) as mobile phase in presence of an internal standard, Fluvastatin [11] and the linearity was observed over the concentration range 0.010-30 µg/ml. Mathrusri Annapurna., *et al.* established a stability indicating liquid chromatographic method [12] for the quantitative determination of Valganciclovir in pharmaceutical dosage forms by using methanol: water: glacial acetic acid (55: 45: 0.1) as mobile phase and the linearity was observed over the concentration range 1 - 200 µg/ml. Rao., *et al.* developed another stability indicating HPLC method [13] for the determination of Valganciclovir in tablet dosage form by using acetonitrile: potassium di hydrogen phosphate buffer solution (pH adjusted to 4.0 with ortho phosphoric acid) (60: 40) as mobile phase and the linearity was observed over the concentration range 0.01-60 µg/ml. Surya Naga Malleswara Rao., *et al.* established a liquid chromatographic method for the determination of chiral purity of (S)-2-azido-3-methylbutanoic acid [14] which is a key raw material of Valganciclovir hydrochloride by using Chiralpak IA column and n-Hexane: Ethanol: Isopropyl alcohol: Trifluoro acetic acid (98: 1.5: 0.5: 0.1) as mobile phase. Suresh Kumar., *et al.* developed a RP-LC method for the impurity profiling and related substances [15] of Valganciclovir hydrochloride using methanol: trifluoro acetic acid as mobile phase and the chromatographic study was carried out on gradient mode.

Katja Heinig., *et al.* determined Ganciclovir and its prodrug Valganciclovir by LC-MS/MS method in human plasma and rat plasma [16] and the linearity was observed as 0.004 - 10 µg/ml. Onkar Singh., *et al.* determined Valganciclovir and Ganciclovir in human plasma by LC/MS/MS [17] using water: trifluoro acetic acid (1M, pH 4.4): methanol (29.9: 0.1: 70) as mobile phase with linearity range 0.005 - 0.8 µg/ml. Xu HR., *et al.* established an assay method using LC/MS/MS for the simultaneous determination of Valganciclovir and its active metabolite Ganciclovir in human plasma [18] using 0.02% formic acid: methanol as mobile phase with linearity range 0.004 - 0.512 µg/ml. S and Barge V developed a stability indicating RP-HPLC method for the determination of Valganciclovir and a LC-MS/MS method for the identification and characterization [19] of forced degradation products of Valganciclovir using acetonitrile: 0.01M potassium dihydrogen ortho phosphate buffer (pH 5.0) (5: 95) as mobile phase. Derangul**a.,** *et al.* developed a LC-MS/MS method [20] for the quantification of Valganciclovir and its active metabolite Ganciclovir in human plasma using 10 mM ammonium acetate in 0.3% formic acid: acetonitrile (35:65) as mobile phase with linearity range 0.002 - 0.805 µg/ml.

This article summarises the analytical techniques proposed by different authors for the quantification of Valganciclovir such as spectrophotometry (Table 1) and RP-HPLC and LC-MS/MS (Table 2) highlighting the significant parameters.

Reagent	Linearity (µg/ml)	λ_{max} (nm)	Comment	Ref
Water	5-60	252.5	Zero order First order	[6]
Phosphate buffer pH 2.0		252		
Phosphate buffer pH 4.0		252		
Phosphate buffer pH 5.0		252		
Methanol	5-30	252	UV region	[7]
Methanol	5-30	254	Very narrow linearity range	[8]
Distilled water	1-6	AUC (247-257)	Low linearity	[9]
Glacial acetic acid with acetous	4-20	-	Titrimetry	[10]
Perchloric acid/Mercuric acetate	4-20	-	Potentiometry	
Potentiometry				
p-dimethylaminobenzaldehyde	5-50	420	Spectrophotometry	

Table 1: Review of spectrophotometric methods.

Mobile phase (v/v)	Column	Linearity (µg/ml)	Remarks	Ref
Liquid chromatographic methods (HPLC)				
Acetonitrile: Methanol: KH_2PO_4 (pH 5.0) (40:20:40) Fluvastatin (Internal standard)	Waters Spherisorb	0.010-30	Human serum	[11]
Methanol: Water: Glacial acetic acid (55: 45: 0.1)	Phenomenex C18	1-200	Stability indicating method	[12]
Acetonitrile: Potassium di hydrogen phosphate (pH adjusted to 4.0 with ortho phosphoric acid) (60: 40)	Symmetry C18	0.01-60	Low linearity range	[13]
n-Hexane: Ethanol: Isopropyl alcohol: Trifluoro acetic acid (98: 1.5: 0.5: 0.1)	Chiralpak IA	–	Chiral purity	[14]
Methanol: Trifluoro acetic acid (Gradient mode)	-	-	Impurity profile and related substances	[15]
Liquid chromatography-Mass spectroscopy methods (LC-MS)				
Mobile phase A: Water: Methanol (15: 85) Mobile phase B: Water: Acetonitrile (10: 90) Both A & B contains 5 mM Ammonium formate and 0.2% Formic acid	Luna Silica	0.004-10	LC-MS/MS Human plasma and Rat plasma	[16]
Water: Trifluoro acetic acid (1M, pH 4.4): Methanol (29.9: 0.1: 70)	Chromolith RP18e	0.005-0.8	LC/MS/MS Human plasma	[17]
0.02% Formic acid: Methanol	Aquasil C18	0.004-0.512	LC/MS/MS Human plasma	[18]
Acetonitrile: 0.01M Potassium dihydrogen ortho phosphate buffer (pH 5.0) (5: 95)	Hypersil Gold C-18	-	LC-MS/MS	[19]
10 mM Ammonium acetate in 0.3 % Formic acid: Acetonitrile (35:65)	Agilent XDB-Phenyl	0.002-0.805	LC-MS/MS Human Plasma	[20]

Table 2: Review of liquid chromatographic methods.

Conclusion

The present review gives an idea about the analytical techniques or methods so far developed for the determination of the anti-viral agent Valganciclovir and its metabolites in pharmaceutical dosage forms as well as in biological fluids.

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