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A REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF VALGANCICLOVIR HYDROCHLORIDE

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ABSTRACT

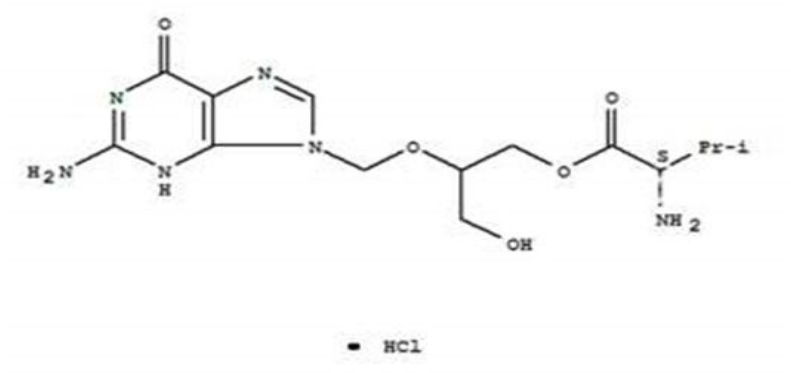
Many theories have proposed to explain the Analytical method development and validation of Valganciclovir hydrochloride. Although the literature survey covers a wide variety of such theories, so the development of sound analytical method is of supreme importance during the process of drug discovery, release to market and development, culminating in a marketing approval. So the objective of this paper is to review the method development, optimize and validation of the method for the Valganciclovir hydrochloride from the development stage of the formulation to commercial batch of the product. So the method development helps in establishment of product specific acceptance criteria and stability of results. Literature survey reveals that the analytical methods based on UV spectrometry, HPLC & HPTLC for the determination of Valganciclovir hydrochloride. The above methods are validated according to ICH guidelines in terms of accuracy, precision, robustness, and other aspects of analytical validation. Although the literature presents these method developments in a variety of contexts, this review article primarily focus on providing simple, sensitive and reproducible Analytical method for the development and validation of Valganciclovir hydrochloride.

KEYWORDS: Valganciclovir hydrochloride, Method Development, Validation, Literature Survey, ICH Guidelines.

INTRODUCTION

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of two diastereomers. Valganciclovir hydrochloride is an antiviral agent that is used to treat

cytomegalovirus retinitis in patients with AIDS, and for the prevention of cytomegalovirus infections in organ transplant recipients who have received an organ from a CMV-positive donor.[1] Valganciclovir works by slowing the growth of the CMV virus. It helps prevent the spread of infection to other areas of the body.[3]



Valganciclovir hydrochloride.[2]

Valganciclovir hydrochloride is available in the form of powder. It is freely soluble in Water, Dimethyl sulfoxide, Methanol, Actonitrile and Actic acid. Valganciclovir hydrochloride is available under the brand name of Valcyte.

REVIEW OF LITERATURE

1. Varun Dasari[4] *et al.,* Have developed a simple, sensitive and economical UV spectrophotometric method for the determination of Valganciclovir in bulk and tablet dosage form. Valganciclovir shows maximum absorbance at 254nm in methanol. Beer's law was obeyed within the concentration range of 5-30 mcg/ml with the correlation Coefficient of 0.9999. The standard plot was clearly showed a straight line passing through the origin. The results of analysis were validated statistically and by recovery studies and found to be satisfactory. The proposed method was extended to pharmaceutical formulations and there was no interference of additives and excipients**.**

2. Sumantha Mondal[5] *et al.,* Have established zero order and first order UV spectrophotometric method using different buffers. Validation study was performed to develop a simple, sensitive, rapid, accurate and economical Ultra Violet spectrophotometric method for the estimation of Valganciclovir. UV 1800 double beam UV Visible Spectrophotometer with a pair of 10mm path length matched quartz cells were used for the study. Method A (Water), Method B (phosphate buffer pH2), Method C (Phosphate buffer pH4) and Method D (phosphate buffer pH5) were developed for estimation of Valganciclovir

by zero-order and first-order derivative. Linearity was carried out in the concentration range of 5-60 µg/ml and the correlation coefficients were found to be 0.999. The percentage recoveries were found to be 98-102%. The relative standard deviation was found to be <2%. The LOD and LOQ were found to be 0.3241µg/ml and 0.8227µg/ml respectively.

3. Bahlul Z Awen[6] *et al.,* A simple, sensitive and economical UV spectrophotometric method has been developed for the determination of Valganciclovir in bulk and tablet dosage form. Valganciclovir shows maximum absorbance at 254 nm in methanol. Beer's law was obeyed within the concentration range of 5-30 mcg/ml with the correlation coefficient of 0.9999. The standard plot was clearly showed a straight line passing through the origin. The results of analysis were validated statistically and by recovery studies and found to be satisfactory. The proposed method was extended to pharmaceutical formulations and there was no interference of additives and excipients.

4. Krishna veni[7] *et al.,* Have developed and validated a specific, accurate, precise and sensitive stability indicating RP HPLC method for the determination of Valganciclovir hydrochloride. An isocratic RP HPLC method was developed with a Hibar C18 (250 X 4.6 mm i.d., 5µ) and methanol: 25mM Ammonium acetate (pH 3.0, adjusted with acetic acid) in the ratio of 10:90 % v/v as mobile phase. The flow rate was maintained at 1 mL min-1 and detection was carried out using PDA detector (254 nm). The drug was subjected to stress conditions of degradation in aqueous solutions including hydrolysis, oxidation and photolysis. Degradation was carried out for 24 hrs at 60°C. The drug was found to degrade extensively under alkaline hydrolysis and oxidation with hydrogen peroxide. Mild degradation was observed in neutral but the drug was stable to photolysis. The developed method was validated with respect to linearity, precision, accuracy, ruggedness and specificity.

5. G. Ramesh[8] *et al.,* A new method has been introduced that is stability indicating RP-HPLC method of Valganciclovir in pure and dosage forms by RP-HPLC was described. Valganciclovir was separated isocratically on an µBondapak® C18 (250 X 4.6 mm), 5µm column with a mobile phase consisting of an isocratic mobile phase containing 0.01M sodium dihydrogen phosphate buffer (pH 5.0) and acetonitrile in the ratio of 600:400 v/v was carried out with the flow rate of 1.2mL/min at ambient column temperature. The effluent was monitored at 254 nm. All the analysis was carried out at 35°C respectively. The developed

RP-HPLC method extensively validated as per ICH standards and the results of the above investigations are included in this part respectively.

6. S. Sawant[9] *et al.,* Valganciclovir was subjected to forced hydrolytic (acidic, alkaline and neutral), oxidative, photolytic and thermal stress in accordance with the ICH guideline Q1A (R2). The drug showed labiality under only acidic and photoacidic conditions while it was stable to other stress conditions. Resolution of the drug and degradation products was achieved on a Hypersil Gold C-18 column (4.6 × 250 mm, 5 µm) utilizing acetonitrile (A) and potassium dihydrogen ortho phosphate buffer (pH 5.0; 0.01M) in the ratio of 5:95 (v/v) at a flow rate of 0.6 ml/min and at the detection wavelength 252 nm. The major acidic stress degradation product was characterized by LC-MS/MS and its fragmentation pathway was proposed. Validation of the LC-DAD method was carried out in accordance with ICH guideline. The method met all required criteria and was applied for analysis of commercially available tablets.

7. G. Kumara Swamy[10] *et al.,* The use of organophosphorus pesticides is widespread in developing countries for increasing the yield of agriculture. It has resulted in increased incidence of ingestion of organophosphorus for self-harm purpose. This study was aimed to assess the pattern and outcome of acute poisoning cases in a tertiary care hospital .Total of 118 patients consisted of 62 males and 56 females in the age group of 14-60 years were studied. Maximum number of 60 patients were in the age group of 25-49 years while 49 patients in age group of 14-24 years and 9 patients in age group of 50 years and above. Higher number of 62 patients were from the rural area while 56 patients had urban background .History of ingestion of pesticide was present in all cases. In 90 patients poison consumption was suicidal in nature while in 28 patients the poisoning was accidental. Phosphomidones was the major culprit in majority of the patients followed by malathion and dichlorophos. 103 recovered and mortality was observed in 15 patients.

8. Goluguri Sunil Reddy[11] *et al.,* have developed ultra-performance liquid chromatography (UPLC) method for the quantitative determination of valganciclovir in bulk and dosage form. The subsequent validation and degradation study was also performed. The chromatographic Separation was achieved with an HSS (100x2.1 mm, 1.8m).column with an isocratic mobile phase containing a mixture of 0.01N potassium dihydrogen orthophosphate and acetonitrile (55:45 v/v). The flow rate of the mobile phase was 0.3 ml/min with a column temperature of 30°C and detection wavelength at 254 nm. The precision of the results, stated as the %RSD

was below 1.0%. The accuracy of the method demonstrated at three levels in the range of 50%, 100% and 150% of the specification limit. The calibration curve was linear over a concentration range from 25 to 150µg/ml with a correlation coefficient of 0.9997. The recovery of valganciclovir was found to be in the range of 98 to 102%, whereas the detection limits were found to be 0.933 and 2.827 µg/ml. The method is validated according to the ICH guidelines and it is applied successfully for the determination of valganciclovir in tablets.

9. M. Mathrusri Annapurna[12] *et al.,* A selective, specific and sensitive stability-indicating high-performance liquid chromatographic method was developed and validated for the determination of Valganciclovir in tablet dosage forms. Reversed-phase chromatography was performed on Shimadzu Model CBM-20A/20 Alite, equipped with SPD M20A prominence photodiode array detector (Isocratic mode) using C18 column (250mm × 4.6 mm, 5µm) with a flow rate of 0.8 mL/min. UV detection was carried at 254 nm. Linearity was observed in the concentration range of 1.0–200µg/ml with regression equation y = 50968 x + 86374 with correlation coefficient of 0.999. The LOQ and LOD were found to be 0.8641µg/ml and 0.2813µg/mL respectively.

10. Ch. Surya Naga Malleswara Rao[13] *et al.,* Have established for simple and accurate normal phase liquid chromatographic method for the determination of chiral purity of (S)-2-azido-3-methylbutanoic acid, S-enantiomer used as key starting raw material in the manufacturing of valganciclovir hydrochloride bulk drug. Chromatographic separation between (S)-2-azido-3-methylbutanoic acid and its opposite enantiomer (R)-2-azido-3-methylbutanoic acid, R-enantiomer was achieved using a Chiralpak IA column using a mobile phase containing n-hexane, ethanol, isopropyl alcohol and tri-fluoro acetic acid (98:1.5:0.5:0.1 v/v/v/v). The resolution between the two enantiomers was found to be more than 2.0. The limit of detection (LOD) and limit of quantification (LOQ) of the Renantiomer was 0.15 and 0.5µg ml-1, respectively, for 10 µL injection volume. The percentage recoveries of the R-enantiomer ranged from 96.5 to 105.3 in the samples of (S)-2-azido-3methylbutanoic acid. The test solution and mobile phase was observed to be stable up to 24 h after the preparation.

11. Sreenivasulu Sura[14] *et al.,* A new simple stability indicating and user friendly RP-Liquid Chromatographic method was developed for the accurate and precise determination of Valganciclovir using Phenomenex Gemini-NX C18 Column (250mm Length × 4.6mm diameter × 5µm particle size) and variable wavelength (UV) detector. The mobile phase used

for the study was sodium Citrate buffer: Methanol in a ratio of 40:60 v/v with a flow rate of 1.0ml/min. Valganciclovir was detected at wavelength 254 nm and eluted at 2.18 ± 0.5min. The developed method is linear over 10-80µg/ml concentration range and correlation co-efficient (r2) obtained as 0.9996. The tailing factor and plate count was found 1.32 and 3649 respectively.

CONCLUSION

Based on above, the literature survey reveals that UV, HPLC and HPTLC methods were published and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus it can be concluded that the reported and published methods can be easily applied for the estimation of the Valganciclovir hydrochloride in pure and pharmaceutical dosage form.

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