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'Elvitegravir' and its Validation: A Review

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Review

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ABSTRACT

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, specific antivirals are used for specific viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead, they inhibit their development. Antiviral drugs are one class of antimicrobials, a larger group that also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs, or antiviral drugs based on monoclonal antibodies. Most antivirals are considered relatively harmless to the host, and therefore can be used to treat infections. They should be distinguished from viricides, which are not medication but deactivate or destroy virus particles, either inside or outside the body. Antivirals also can be found in essential oils of some herbs, such as eucalyptus oil and its constituents.

INTRODUCTION

Many antiviral drugs work by interfering with replication of viruses. Most drugs used to treat human immunodeficiency virus (HIV) infection work this way. [1, 2] Because viruses are tiny and replicate inside cells using the cells own metabolic functions, there are only a limited number of metabolic functions that antiviral drugs can target. In contrast, bacteria are relatively large organisms, commonly reproduce by themselves outside of cells, and have many metabolic functions that antibacterial drugs (antibiotics) can target. [3-6] Therefore, antiviral drugs are much more difficult to develop than antibacterial drugs. [6-10] Also, unlike antibiotics, which are usually effective against many different species of bacteria, most antiviral drugs are usually effective against only one (or a very few) viruses. Antiviral drugs can be toxic to human cells. Also, viruses can develop resistance to antiviral drugs. [15-20]

Other antiviral drugs strengthen the immune response to the viral infection. These drugs include several types of interferons, immunoglobulins, and vaccines:

- Interferon drugs are replicas of naturally occurring substances that slow or stop viral replication. [21]
- Immune globulin is a sterilized solution of antibodies (also called immunoglobulins) collected from a group of people. [22]
- Vaccines are materials that help prevent infection by stimulating the body's natural defense mechanisms (see Immunization). [23-26]

Elvitegravir

Traditional drug

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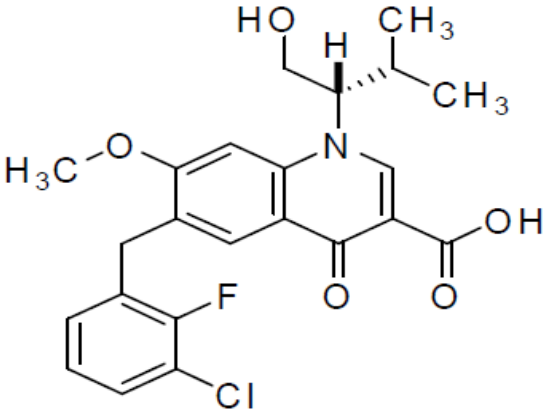
Elvitegravir is a member of the integrase inhibitor class of antiretroviral compounds. Integrase inhibitors block the ability of HIV to integrate into the genetic material of human cells. Elvitegravir was licensed by Gilead from Japan Tobacco Inc. (JT) in March 2005. Under the terms of Gilead's agreement with JT, Gilead has exclusive rights to develop and commercialize elvitegravir in all countries of the world, excluding Japan, where JT retains rights. [27-30]

Evolution of Elvitegravir

The U.S. Food and Drug Administration (FDA) has approved Vitekta (elvitegravir), an integrase strand transfer inhibitor for the combination treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-experienced adults. The U.S. Food and Drug Administration (FDA) has approved Vitekta (elvitegravir), an integrase strand transfer inhibitor for the combination treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-experienced adults. Elvitegravir is an HIV integrase strand transfer inhibitor that works by interfering with one of the enzymes that HIV needs to multiply. [31-35] It is indicated in combination with an HIV protease inhibitor coadministered with ritonavir and with other antiretroviral drugs. It is one of the ingredients in the combination HIV drug Stribild, which was approved by the FDA in August, 2012. Vitekta (elvitegravir) comes in 85 mg and 150 mg tablets. It is administered once daily with food. The approval of Vitekta is based on the analyses through 96 weeks from one randomized, double-blind, active-controlled trial, Study 145, in treatment-experienced, HIV-1 infected subjects (N=702). In Study 145, subjects were randomized in a 1:1 ratio to receive either Vitekta (150 mg or 85 mg) once daily or raltegravir 400 mg twice daily, each administered with a background regimen (BR) containing a fully active protease inhibitor coadministered with ritonavir and a second antiretroviral drug. The BR was selected by the investigator based on genotypic/phenotypic resistance testing and prior antiretroviral treatment history. Virologic outcomes were similar across the treatment arms through 96 weeks. The most common side effects of Vitekta observed in clinical trials were diarrhea, nausea and headache. [36-40]

Drug Profile

Table 1: Structural Features of Elvitegravir

Official name	Chemical Name(s)	Structure
Elvitegravir	6-[(3-Chloro-2-Fluorophenyl) methyl]-1-[(2S)-1-Hydroxy-3-Methylbutan-2-yl]-7-Methoxy-4-Oxoquinoline-3 Carboxylic Acid (OR) 6-[(3-chloro-2-fluorophenyl)-methyl]-1,4-dihydro-1-[(1S)-1-(hydroxymethyl)-2-methyl propyl]-7-methoxy-4-oxo-.	

Application : Elvitegravir is a Human Immunodeficiency Virus Integrase Strand Transfer Inhibitor.
Purity : ≥99%
Molecular Weight : 447.883823 g/mol
Molecular Formula : $C_{23}H_{23}ClFNO_5$
Physical State : white to pale yellow solid
Solubility : less than 0.3 µg/mL in water at 20°C

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Melting Point : 92-96 °C
Therapeutic category : Anti-viral

Elvitegravir, the second integrase inhibitor that will be submitted for regulatory approval appears to be a promising once-daily agent when combined with other antiretroviral drugs. Elvitegravir is administered as a once-daily integrase inhibitor that needs boosting by either ritonavir or cobicistat. Clinical studies in experienced patients have assessed both ritonavir and cobicistat as booster; Elvitegravir is being tested as first-line drug in a fixed-dose combination ("Quad") including tenofovir, emtricitabine, cobicistat and Elvitegravir. Quad was submitted to the US Food and Drug Administration for regulatory approval for use in naive patients in late 2011. [41-47] Elvitegravir (also known as GS-9137 or JTK-303) has the chemical name 6-(3-chloro-2-fluorobenzyl)-1-[(2S)- 1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4- dihydroquinoline-3-carboxylic acid], a molecular weight of 447.88 g/mol, and the molecular formula $C_{23}H_{23}ClFNO_5$.It is part of the integrase inhibitor class of drugs that work by inhibiting HIV-1 strand transfer and integration. Integrase is one of the three enzymes required of HIV replication. Its primary role is to integrate the viral DNA into the cellular DNA of the host. Elvitegravir inhibits the integrase enzyme at thisvital step, blocking viral DNA strand transfer and integration, allowing it to be metabolized by cellular enzymes. The lack of a functionally equivalent enzyme to integrase in human cells reduces the potential for drug-induced cytotoxicity.

Mechanism of action

Elvitegravir is a HIV-1 (integrase strand transfer inhibitor INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II. The antiviral activity of Elvitegravir with antiretroviral drugs in two-drug combination studies was additive to synergistic when combined with NRTIs (abacavir, didanosine, emtricitabine, 3TC, d4T, tenofovir, or AZT); NNRTIs (efavirenz, etravirine, or nevirapine); protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir); the integrase strand transfer inhibitor raltegravir; the fusion inhibitor enfuvirtide, or the CCR5 co-receptor antagonist, maraviroc. Elvitegravir is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. Elvitegravir does not inhibit human topoisomerases I or II. [48-50]

Description

Elvitegravir is a Human Immunodeficiency Virus Integrase Strand Transfer Inhibitor. Used in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV). It is an antiviral.

Pharmacokinetics

Absorption

Following oral administration of VITEKTA and ritonavir with food, in HIV-1 infected subjects, peak elvitegravir plasma concentrations were observed approximately 4 hours post-dose. The steady-state mean elvitegravir pharmacokinetic parameters. Elvitegravir plasma exposures increased in a less than dose proportional manner, likely due to solubility-limited absorption.

A high fat meal did not affect the Cmax and AUC of oral Elvitegravir. Therefore, VITEKTA (Elvitegravir tablets) Tablets must be taken with food.

Distribution

Elvitegravir is 98–99% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 ng/mL to 1.6 µg/mL. The mean plasma-to-blood drug concentration ratio is 1.37. [51-55]

Metabolism

Elvitegravir undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. Following oral administration of [14C]elvitegravir/ritonavir, elvitegravir was the predominant species in plasma, representing ~94% of the circulating radioactivity. Aromatic and aliphatic hydroxylation or glucuronidation metabolites were present in very low levels, displayed considerably lower anti-HIV activity and did not contribute to the overall antiviral activity of elvitegravir. [56-60]

Elimination

Following oral administration of [14C]elvitegravir/ritonavir, 94.8% of the dose was recovered in feces, consistent with the hepatobiliary excretion of elvitegravir; 6.7% of the administered dose was recovered in urine as metabolites. The median terminal plasma half-life of elvitegravir following administration of VITEKTA and ritonavir was approximately 8.7 hours. [61-65]

Pharmacodynamics

The effect of multiple doses of elvitegravir 125 mg (1.5 times the lowest recommended dosage) and 250 mg (1.7 times the maximum recommended dosage) (coadministered with 100 mg ritonavir) on QT interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel group thorough QT study in 126 healthy subjects. No clinically meaningful changes in QTc interval were observed with either 125 mg dose or the 250 mg dose. The dose of 250 mg elvitegravir (with 100 mg ritonavir) is expected to cover the high exposure clinical scenario. [66-70]

Adverse effects [71]

- Abdominal dreams
- Headache
- Bloated
- Full feeling
- Passing gas
- Trouble sleeping
- Unusual drowsiness
- Chills
- Constipation
- Indigestion
- Lack and lose of strength
- Pain in the stomach, side, or abdomen, possibly radiating to the back

Uses

This medication is used to prevent nausea and vomiting caused by cancer chemotherapy. It may also be used to prevent nausea and vomiting after surgery. [72-73]

Comparison of Elvitegravir with other Drugs

Based on drug interaction studies conducted with elvitegravir, no clinically significant drug interactions have been either observed or expected when elvitegravir is combined with the following drugs: abacavir, darunavir, emtricitabine, etravirine, fosamprenavir, maraviroc, stavudine, tipranavir, tenofovir disoproxil fumarate, zidovudine; H2-receptor antagonists such as famotidine; proton-pump inhibitors such as omeprazole; and the HMG-CoA reductase inhibitors atorvastatin, pravastatin, and rosuvastatin. When any of the above drugs are used concomitantly with VITEKTA in combination with a protease inhibitor coadministered with ritonavir, consult the prescribing information of the protease inhibitor for dosing recommendation for these drugs. [74]

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Generic companies

The generic elvitegravir is manufactured by 1 company

Vitekta from Gilead Sciences [Elvitegravir]

Name of the Tablet	Constituent	Strength
Vitekta	Elvitegravir	85 mg or 150 mg

Below are some of the details of elvitegravir

The U.S. Food and Drug Administration (FDA) have approved Vitekta (elvitegravir), an integrase strand transfer inhibitor for the combination treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-experienced adults. Elvitegravir is an HIV integrase strand transfer inhibitor that works by interfering with one of the enzymes that HIV needs to multiply. It is indicated in combination with an HIV protease inhibitor coadministered with ritonavir and with other antiretroviral drugs. It is one of the ingredients in the combination HIV drug Stribild, which was approved by the FDA in August, 2012. [75]

Marketed formulations worldwide

A novel HIV integrase inhibitor, JT's original compound elvitegravir (JTK-303), has been approved by the European Medicines Agency (EMA). The drug is to be marketed as Vitekta™ in the European Union. Japan Tobacco Inc. (JT) (TSE:2914) announced that a statement has been issued to this effect by Gilead Sciences, Inc. (Gilead) of Foster City, California. Elvitegravir interferes with HIV replication by blocking the ability of the virus to integrate into the genetic material of human cells. The Company licensed elvitegravir to Gilead in March 2005 with exclusive rights to develop and commercialize the drug worldwide, excluding Japan. Prior to the approval of elvitegravir as a standalone agent, a once-daily single tablet regimen which contains four compounds: elvitegravir 150mg; cobicistat 150mg; emtricitabine 200mg; and tenofovir disoproxil fumarate 300mg, was provided to HIV patients in the United States, the European Union, Japan and other countries. Torii Pharmaceuticals Co., Ltd., JT's pharmaceutical subsidiary, has marketed this drug as Stribild® Combination Tablets in Japan, while Gilead has marketed this drug as Stribild® outside Japan. The U.S. Food and Drug Administration today approved Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate), a new once-a-day combination pill to treat HIV-1 infection in adults who have never been treated for HIV infection. Stribild contains two previously approved HIV drugs plus two new drugs, elvitegravir and cobicistat. Elvitegravir is an HIV integrase strand transfer inhibitor, a drug that interferes with one of the enzymes that HIV needs to multiply. Cobicistat, a pharmacokinetic enhancer, inhibits an enzyme that metabolizes certain HIV drugs and is used to prolong the effect of elvitegravir. The combination of emtricitabine and tenofovir disoproxil fumarate, approved in 2004 and marketed as Truvada, blocks the action of another enzyme that HIV needs to replicate in a person's body. Together, these drugs provide a complete treatment regimen for HIV infection. [76-80]

Market statistics

The 'Global and Chinese Elvitegravir Industry, 2009-2019 Market Research Report' is a professional and in-depth study on the current state of the global Elvitegravir industry with a focus on the Chinese market. The report provides key statistics on the market status of the Elvitegravir manufacturers and is a valuable source of guidance and direction for companies and individuals interested in the industry. [81]

Firstly, the report provides a basic overview of the industry including its definition, applications and manufacturing technology. Then, the report explores the international and Chinese major industry players in detail. In this part, the report presents the company profile, product specifications, capacity, production value, and 2009-2014 market shares for each company. Through the statistical analysis, the report depicts

the global and Chinese total market of Elvitegravir industry including capacity, production, production value, cost/profit, supply/demand and Chinese import/export. The total market is further divided by company, by country, and by application/type for the competitive landscape analysis. The report then estimates 2014-2019 market development trends of Elvitegravir industry. Analysis of upstream raw materials, downstream demand, and current market dynamics is also carried out. In the end, the report makes some important proposals for a new project of Elvitegravir Industry before evaluating its feasibility. Overall, the report provides an in-depth insight of 2009-2019 global and Chinese Elvitegravir industry covering all important parameters. [82-85]

Future scope

Elvitegravir is also effective against such drug-resistant strains of HIV. In a Phase II study that ran for 48 weeks, elvitegravir when taken as part of combination therapy was effective in significantly reducing viral load in treatment-experienced patients. Researchers have also conducted a randomized placebo-controlled study comparing elvitegravir to raltegravir in treatment-experienced people. After one year, elvitegravir was found to be roughly equivalent to raltegravir in its effectiveness.

Clinics in Canada, Australia and the U.S. screened 1,335 HIV-positive volunteers to find potential participants for this clinical trial. Eligible volunteers were randomly assigned to one of the following study groups: elvitegravir 150 mg and ritonavir 100 mg, both drugs once daily + background regimen. [86-90]

Validation of Elvitegravir

Padigela sweta et al [91] has developed a simple, precise, rapid and accurate RP- HPLC method was developed for the estimation of Elvitegravir (EVG) in tablet dosage forms. An Inertsil ODS 3V, 250x4.6 mm, column with 5 µm particle size and the Mobile Phase consisting of 0.03M KH_2PO_4 in water adjusting the pH-3.2 with dilute O-Phosphoric Acid mixed in Methanol & Water in ratio of 80:20 v/v & Acetonitrile & Buffer in ratio of 60:40 v/v, was used as a diluent in the gradient mode. The flow rate was 1.0 ml/min and the effluents were monitored at 257 nm. The retention time was 6.250 min and the detector response was linear in the concentration range of 80-960 µg/mL for EVG successively. The respective linear regression equation being Y= 9474.289x + 147734.8116 for EVG. The Limit of Detection (LOD) & The Limit of Quantification (LOQ) was found to be 0.4 & 1.2 µg for EVG. The percentage assay of EVG was 98.60%. The method was validated by determining its accuracy, precision and system suitability. The results of the study showed that the proposed RP-HPLC method is simple, rapid, precise and accurate, which is useful for the routine determination of EVG in bulk drug and in its pharmaceutical dosage forms.

Aouri M et al [92] has developed a validated assay by liquid chromatography-tandem mass spectrometry for the simultaneous quantification of Elvitegravir and rilpivirine in HIV positive patients. Because of the large variability in the pharmacokinetics of anti-HIV drugs, therapeutic drug monitoring in patients may contribute to optimize the overall efficacy and safety of antiretroviral therapy. An LC-MS/MS method for the simultaneous assay in plasma of the novel antiretroviral agentsrilpivirine (RPV) and Elvitegravir (EVG) has been developed to that endeavor. Plasma samples (100µL) extraction is performed by protein precipitation with acetonitrile, and the supernatant is subsequently diluted 1:1 with 20-mM ammonium acetate/MeOH 50:50. After reverse-phase chromatography, quantification of RPV and EVG, using matrix-matched calibration samples, is performed by electrospray ionization-triple quadrupole mass spectrometry by selected reaction monitoring detection using the positive mode. The stable isotopic-labeled compounds RPV-(13) C6 and EVG-D6 were used as internal standards. The method was validated according to FDA recommendations, including assessment of extraction yield, matrix effects variability (<6.4%), as well as EVG and RPV short and long-term stability in plasma. Calibration curves were validated over the clinically relevant concentrations ranging from 5 to 2500ng/ml for RPV and from 50 to 5000ng/ml for EVG. The method is precise (inter-day CV%: 3-6.3%) and accurate (3.8-7.2%). Plasma samples were found to be stable (<15%) in all considered conditions (RT/48h, +4°C/48h, -20°C/3months and 60°C/1h). Selected metabolite profiles analysis in patients' samples revealed the presence of EVG glucuronide that was well separated from parent EVG, allowing excluding potential interferences through the in-source dissociation of glucuronide to parent drug. This new, rapid and robust LCMS/MS assay for the simultaneous

quantification of plasma concentrations of these two major new anti-HIV drugs EVG and RPV offers an efficient analytical tool for clinical pharmacokinetics studies and routine therapeutic drug monitoring service.

Fourati S et al [93] The objectives of this study were to determine the prevalence and patterns of resistance to integrase strand transfer inhibitors (INSTIs) in patients experiencing virological failure on raltegravir-based ART and the impact on susceptibility to INSTIs (raltegravir, elvitegravir and dolutegravir).Data were collected from 502 treatment-experienced patients failing a raltegravir-containing regimen in a multicentre study. Reverse transcriptase, protease and integrase were sequenced at failure for each patient. INSTI resistance-associated mutations investigated were those included in the last ANRS genotypic algorithm (v23).Among the 502 patients, at failure, median baseline HIV-1 RNA (viral load) was 2.9 log10 copies/mL. Patients had been previously exposed to a median of five NRTIs, one NNRTI and three PIs. Seventy-one percent harboured HIV-1 subtype B and the most frequent non-B subtype was CRF02_AG (13.3%). The most frequent mutations observed were N155H/S (19.1%), Q148G/H/K/R (15.4%) and Y143C/G/H/R/S (6.7%). At failure, viruses were considered as fully susceptible to all INSTIs in 61.0% of cases, whilst 38.6% were considered as resistant to raltegravir, 34.9% to elvitegravir and 13.9% to dolutegravir. In the case of resistance to raltegravir, viruses were considered as susceptible to elvitegravir in 11% and to dolutegravir in 64% of cases. High HIV-1 viral load at failure (P<0.001) and low genotypic sensitivity score of the associated treatment with raltegravir (P<0.001) were associated with the presence of raltegravir-associated mutations at failure. Q148 mutations were selected more frequently in B subtypes versus non-B subtypes (P = 0.004).This study shows that a high proportion of viruses remain susceptible to dolutegravir in the case of failure on a raltegravir-containing regimen.

Raffe S [94] Co-formulated elvitegravir, cobicistat, emtricitabine and tenofovir (EVG/COBI/FTC/TDF or StribildTM) is the latest antiretroviral tablet approved in the EU. This review aims to provide an overview of its role in the management of HIV-1 infection. Areas covered: This review covers material searched and obtained through Medline and Pubmed up to July 2014. Expert opinion: Antiretroviral treatment prevents the progressive destruction of the immune system by the HIV, significantly reducing morbidity and mortality. The efficacy and tolerability of EVG/COBI/FTC/TDF compared to current standard of care as a single-tablet treatment choice has been shown in study 102 and study 103. Its use is restricted to patients without significant pre-existing renal impairment and may be limited by concomitant medications but undoubtedly increases treatment choice for HIV-1-infected adults. [95-100]

As per above studies there are some methods developed for the estimation of Elvitegravir. It was found that the retention times are high in some methods. The methods developed for the Elvitegravir are highly economical which are high performance liquid chromatography-ultra violet (HPLC-UV), liquid chromatography-tandem mass spectrometric (LC-MS/MS). [111-113]

Therefore an attempt was made to develop and validate a simple and economical RP-HPLC method as per ICH guidelines for the estimation of Elvitegravir.

CONCLUSION

There is only one report on the HPLC determination of Elvitegravir in pharmaceutical formulations in the literature prior to commencement of this work. It is a sensitive, accurate and precise HPLC for the estimation of Elvitegravir in bulk drug. In comparison with already existing method, the current method of analysis is more sensitive and selective and linear in low concentration levels. From the typical chromatogram of Elvitegravir as shown in fig 4.1, it was found that the retention time was 10.41 min. The contents of the mobile phase were aqueous Potassium dihydrogen phosphate buffer adjusted pH at 3.2 with o-phosphoric acid (mobile phase solvent-A) and acetonitrile (mobile phase solvent-B) in a gradient mode of separation was used to resolute the Elvitegravirat a flow rate of 1.0 ml/min was found to be most suitable to obtain a peak well defined and free from tailing. In the present developed HPLC method, the

standard and sample preparation required less time and no tedious extraction were involved. A good linear relationship was observed between the concentration range of 15-180µg/mL. The assay of Elvitegravir in bulk was found to be 99.25%. From the recovery studies it was found that about 99.35 % on average of Elvitegravir was recovered which indicates high accuracy of the method. The absence of additional peaks in the chromatogram indicates non-interference of the common excipients used in the sterile powder for injection. This demonstrates that the developed HPLC method is simple, linear, accurate, sensitive and reproducible. Thus, the developed method can be easily used for the routine quality control of bulk and sterile powder for injection dosage form of Elvitegravir within a short analysis time. It can be seen from the results presented that the proposed procedure has good precision and accuracy. Results of the analysis of pharmaceutical formulations revealed that proposed methods are suitable for their analysis with virtually no interference of the usual additives present in the pharmaceutical formulations. The above proposed method obviates the need for any preliminary treatment and is the method could be of use for process development as well as quality assurance of Elvitegravir bulk drugs.

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