Review Article

Analytical Techniques for Dolutegravir: A Review

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ABSTRACT

A review is presented on different analytical techniques used for qualitative and quantitative analysis of Dolutegravir, which is used as an antiretroviral drug. Efforts have been made to collate all the relevant references to the extent possible. The review discusses the cited analytical techniques which will help to give insights into various method development of the drugs in pure and dosage form. The review highlights the basics as well as advanced techniques performed for estimating Dolutegravir. The techniques here have been demonstrated to be useful for qualitative and quantitative determination of Dolutegravir and may find application in routine analysis. Analytical method development and validation is an important area during the development of drug substituents and drug products in pharmaceutical industry. To make drugs serve their purpose various chemical and instrumental methods are involved in the estimation of drugs. These pharmaceutical products may develop impurities at various stage of their development and storage which makes the products hazardous to be administered thus they may be detected and quantitated. For this analytical instrumentation and methods plays an important role. This review foregrounds the role of analytical methods in assessing the quality of drugs. The review highlights published analytical methods reported so far in the literature for the determination of Dolutegravir in biological samples and pharmaceutical formulations.

Keywords: Dolutegravir, Antiretroviral, Qualitative analysis, Quantitative analysis.

INTRODUCTION

Dolutegravir is a HIV-1 integrase inhibitor that blocks the strand transfer step of the integration of the viral genome into the host cell (INSTI.[1] The effect of this drug has no homology in human host cells which give it an excellent tolerability and minimal toxicity.[2] Dolutegravir was developed by ViiV Healthcare and FDA approved on august 12,2013.[3] On November 21,2017, Dolutegravir, in combination with Rilpivirine was approved as part of the first complete treatment regimen with only two drugs for the treatment of adults with HIV-1 named Juluca.[4] Common side effects of Dolutegravir in clinical trials included insomnia and headache.[4] Serious side effects included allergic reactions and abnormal liver function in patients who were also infected with hepatitis B or C. There is tentative concerns that use during pregnancy can result in harm to baby.[9] It is unclear if use during breastfeeding is safe.

Dolutegravir was approved for medical use in the United States in 2013.[8] It is on the WHO´s list of Essential medicines, the most effective and safe medicine needed in a health system. [10]

Pharmacodynamics

HIV-1 infected subject on Dolutegravir monotherapy demonstrated rapid and dose-dependent reduction of antiviral activity with declines of HIV-1 RNA copies per ml. The antiviral response was maintained for 3 to 4 days after the last dose. [5] The sustained response obtained in clinical trials indicates that Dolutegravir has a tight binding and longer dissociative half- life providing it a high barrier to resistance. The combination therapy (ripivirine and dolutegravir) presented the same viral suppression found in previous three-drug therapies without intergrase strand transfer inhibitor mutations or ripivirine resistance.

Mechanism of Action

Dolutegravir is an HIV-1 Antiviral agent. It inhibits HIV integrase by binding to the active site and blocking the strand transfer step of retroviral DNA integration in the host cell. The strand transfer step is essential in the HIV replication cycle and results in the inhibition of viral activity. Dolutegravir has a mean EC50 value of 0.5nM (0.21ng/mL) to 2.1nM(0.85ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.[6]

Pharmacokinetics

When 50 mg of Dolutegravir once daily was orally administered to HIV-1 infected adults, the AUC, C_{max} and C_{min} is 53.6mcg/mL, 3.67mcg/mL, and 1.11mcg/mL, respectively. The peak plasma concentration was observed 2 to 3 hours post- dose. Steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C_{24}h ranging from 1.2 to 1.5.When 50 mg once daily is given to pediatric patients (12 to <18 years and weighing ≥40 kg) the C_{max}, AUC, and C24 is 3.49mcg/mL, 46mcg/mL, and 0.90mcg/mL respectively. [1]

The administration of a dose of 50 mg of Dolutegravir presents an apparent volume of distribution of 17.4L.[1] The median dolutegravir concentration in CSF was

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18ng/mL after 2 weeks of treatment. [1] Dolutegravir is highly protein bound to human plasma proteins reaching a percentage 98.9% of the administered dose.[1] Dolutegravir is highly metabolized through three main pathways and it forms no long –lived metabolites. The first pathway is defined by the glucoronidation by UGT1A1, the second pathway by carbon oxidation by CYP3A4 and the third pathway is what appears to be a sequential oxidative deflourinatioin and glutathione conjugation. The main metabolite found in blood plasma is the ether glucoronide form (M2) and its chemical properties disrupt its ability to bind metal ions, therefore it is inactive. [6]

When a single dose of dolutegravir is given, nearly all complete dose is recovered in a proportion of 53% excreted unchanged in the feces and 31% excreted in urine. The renal eliminated recovered dose consists of ether glucoronide of Dolutegravir (18.9%), a metabolite formed by oxidation at the benzylic carbon (3.0%), a hydrolytic N- dealkylation product (3.6%) and unchanged drug (<1%). The half- life of dolutegravir is 14 hours. [6] Dolutegravir is indicated in combination with other antiretroviral agents for the treatment of patients with HIV-1 infection that comply with the characteristics of being adults or children aged 12 years and older and present at least a weight of 40kg. [7] The FDA combination therapy approval of dolutegravir and rilpivirine is indicated for adults with HIV-1 infections whose virus is currently suppressed (<50 copies/mL) on a stable regimen for at least six months, without history of treatment failure and no known substitutions associated to resistance to any of the two components of the therapy.[4]

Numerous methods have been published for the analysis of Dolutegravir and in this present literature the utilization of HPLC, HPTLC UV, UPLC, LC/MS methods bioanalytical techniques for the quantitative determination of antiretroviral drugs were reviewed.

Quantitative Analytical Techniques for Dolutegravir

Analytical techniques for quantitative analysis help to accurately determine the concentration of individual component present in the sample.

Spectroscopic Techniques

A method which find an important place in pharmacopoeias are spectrophotometric methods based on UV absorption and chemical reactions. Spectrophotometry is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength.

The advantage of these methods is low time and labour consumption. The precision and accuracy of these methods is also excellent. The use of UV-vis spectrophotometry especially applied in the method development of pharmaceutical dosage form has increased rapidly over the last few years because of its ease of use.

Most of what we know about the structure of atoms and molecules comes from studying their interaction with light (EMR) different. Regions of EMR spectrum provide different kind of information as a result of such interaction.

Advantages of Spectroscopic Techniques

- Rapid analysis: information is available in a matter of seconds as compared to minutes or even hours in other conventional techniques.
- Nondestructive: most spectroscopic methods are non-destructive in nature and there is 100% recovery of sample after analysis.
- Micro analysis: generally, the methods can be adapted to micro volume anlaysis when quantity of sample is limited.

Several approaches using spectrophotometry for determination of active pharmaceutical ingredients in bulk and formulations have been reported and details of these methods are as follows.

1. UV Method

Bhavar Girija Balasaheb et al[11] illustrated an accurate, precise spectrophotometric method for quantitative analysis of Dolutegravir sodium in tablet formulation. The initial stock solution of Dolutegravir sodium was prepared in methanol solvent followed by dilution with water. At the wavelength of 259.80nm. The standard solution of Dolutegravir sodium in water has shown maximum absorbance. Dolutegravir in the range of 5 - 40µg/mL has obeyed Beer-Lambert's law. with coefficient of correlation (R^2) was 0.9992.

A novel UV method for the determination of Dolutegravir using 8M urea as solubilizing agent was cited by Masthanamma et al[12]. Concentrated aqueous hydrotropic solution of sodium benzoate, Urea, sodium salicylate, nicotinamide, sodium ascorbate and sodium glycinate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs. In the present investigation hydrotropic solubilization technique has been employed to solubilize the poorly water soluble anti-retroviral drug Dolutegravir. Determination of solubilities of drug in 8M urea hydrotropic solution and distilled water was carried at room temperature. There was more than 50-fold enhancement in aqueous solubility of Dolutegravir with 8M urea. Therefore, it was thought worthwhile to solubilize the poorly water soluble Dolutegravir from fine powder of its laboratory mixture to carryout spectrophotometric analysis at 258nm in method A, 248-268nm in method Band 256nm in method C. Urea does not show any absorbance above 250nm. Beer's law was obeyed in the concentration range of 52.5- 20µg/ml in method A, B and C with correlation coefficient (R^2) of 0.996, 0.995 and 0.996 respectively.[12]

Srinivasan et al[13] has developed a method for the quantitative analysis of Dolutegravir sodium in tablet

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formulations. The initial stock solution of Dolutegravir sodium was prepared in methanol solvent and subsequent dilution was done in water. The standard solution of Dolutegravir sodium in water showed maximum absorption at wavelength 259.80nm. The drug obeyed Beer's lamberts law in the concentration range of 5-40µg/ml with coefficient of correlation (R^2) was 0.9992.

2. Chromatograph Techniques HPLC and HPTLC

HPLC provides reliable quantitative precision and accuracy for the determination of the active pharmaceutical ingredients and related substances in the same run using a variety of columns, solvents and detectors and can be HPLC METHOD performed on fully automated instrumentation. HPLC provides excellent reproducibility and is applicable to a wide range of compound types by judicious choice of HPLC column chemistry. Separation of chiral molecules into their respective enantiomers is also possible by HPLC. HPLC, particularly reversed phase HPLC is currently the, most suitable method for meeting most of the criteria for quantitative analysis of a number of drugs. It is basically a liquid chromatographic technique involving separation of complex mixtures and quantification of the resolved components. The separation may be by adsorption, partition, exclusion or ion-exchange depending on the type of the stationary phase packed in the column.

Girija B.Bhavar et al[17] has developed a simple, precise and specific high performance liquid chromatographic (HPLC) and high performance thin layer chromatography (HPTLC) methods for determination of Dolutegravir sodium in bulk drug and pharmaceutical dosage form.

In HPLC method, drug was analysed using ODS C_{18} column (150×4.6mm, 5µm particle size) using a mixture of acetonitrile: water (pH 7.5) in the ratio 80:20 v/v as the mobile phase at a flow rate of 1mL/min. The wavelength is measured at 260nm.At the concentration range of 5-35µg/mL, the method was found to be linear. The peak was noticed at 3.0 ± 0.1 minutes.

HPTLC METHOD

With the advancement of the technique, high performance thin layer chromatography (HPTLC) emerged as an important instrument in drug analysis. HPTLC is a fast separation technique and flexible enough to analyze a wide variety of samples. This technique is advantageous in many means as it is simple to handle and requires a short analysis time to analyze the complex of the crude sample cleanup. HPTLC evaluates the entire chromatogram with a variety of parameters without time limits. Moreover, there is simultaneous but independent development of multiple samples and standards on each plate, leading to an increased reliability of results. HPTLC has been used to quantitate drugs as ethinyl estradiol and cyposterone, alfuzosin and tramadol and pentazocine.

In HPTLC method, analysis was carried out on aluminium-packed plates pre-coated with silica gel G60 F254 using methanol:chloroform:formic acid in the proportion of 8:2:0.5 v/v/v as the mobile phase. The solvent system found to produce compact spots with *Rf* value of 0.77±0.01. At 265nm, densitometric analysis of Dolutegravir sodium was done.

Reverse Phase Chromatography

In 1960s the chromatographic operators started modifying the column material silanol polar groups by silica with organic silica or with organic silanes chemically. The aim was to make a non polar or less polar column material so that water soluble polar compounds can be separated using polar solvents. Since the iconic nature of the modified silica is now reversed chemically i.e; the nature of the phase is non polar. The separation carried out with such silica is called as 'reverse phase chromatography'.

Chemically bonded stationary phases based on silica are commercially available in large number. In reverse phase chromatography, chemically modified silica based stationary phases are popular. Other absorbents based on polymer (styrene-divinyl benzene co-polymer) are slowly becoming popular.

Less water-soluble compounds are retained on the modified stationary phase. The retention decreases in the following order: aliphatic > induced dipole(CCL4) > permanent dipoles > weak lewis acids (ethers, aldehydes, ketones) > strong lewis acids (carboxylic acids).

RP-HPLC method development and validation for the simultaneous determination of Lamivudine, Abacavir and Dolutegravir in pharmaceutical dosage form has been performed by Rajkumar prava et al[18] which involved the use of inertsil ODS C_{18} (250×4.6mm,5m) column as the stationary phase. The mobile phase used was Phosphate buffer (pH 3.0), Acetonitrile, methanol in the ratio 50:20:30%v/v/v at a flow rate of 1.0 mL/min. Retention times of Lamivudine, Abacavir and Dolutegravir were found to be 2.2min, 2.9min &7.4min respectively.

Yashpalsinh N et al[19] has demonstrated the development and validation of chiral RP-HPLC method for quantification of optical isomers in Dolutegravir Sodium. He has described simple, specific RP-HPLC method for the separation of (R,R)- diasteromer,(S,S)-diastereomer and (S,R) enantiomer of Dolutegravir from its process related and degradant impurities using Chiralpak IF-3,3µm (250mm×4.6mm) HPLC column.

Agilent HPLC 1200 equipped with photodiode array detector was used. The mobile phase used is combination of mixing buffer and solvent mixture in the ratio of 63:37 (mixing buffer: 0.01 mol potassium dihydrogen orthophosphate aqueous solution adjusted to pH 2.0 with orthophosphoric acid used as buffer and the solvent mixture consists of tertiary butyl methyl ether and acetonitrile in the ratio 10:35 v/v).For the determination of enantiomeric purity and quantification of isomers, sample solution of concentration of 500 µg/ml-1 was

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prepared. The flow rate was maintained at 1.0ml/min. The operations was carried out at 260 nm by using HPLC software photodiode array detector.

Nagasarappu Mallikarjuna Rao[20] has illustrated HPLC method for determination of Lamivudine, Tenofovir and Dolutegravir in bulk and their tablet dosage form. A reverse phase gradient programming has been done with reverse phase C $_{18}$ column (250×4.6mm,5 micron) with a flow rate 1mL/min, detected at 260nm. Buffer used is 0.05M Phosphate buffer pH 6.2 ± 0.05 adjusted with dilute potassium hydroxide solution and acetonitrile was used as mobile phase. The mean retention time of Lamivudine, Tenofovir and Dolutegravir were found to be 2.8,5.2 and 11.5 min respectively and the linearity values were found to be 27-162 µg/mL, 27-162 µg/mL and 4.5 - 28 µg/mL respectively.

Simultaneous HPLC method development and validation for estimation of Lamivudine, Abacavir and Dolutegravir in combined dosage form with their stability studies has been performed by Narottam Pal et al.[21] The method was established with non polar –kromasil 250 mm× 4.5mm,5 µm, buffer: acetonitrile in the ratio 65:35 is used as mobile phase at a flow rate of 1mL/min, temperature was maintained at 30°C. Retention times for the three compounds were found to be 2.250 min, 2.74 min, and 9.633 for Lamivudine, Abacavir and Dolutegravir. The linearity range was between 15 to 90 ppm, 30 to 180 ppm and 2.5 to 15 ppm, the values of LOD were 0.08µg/mL, 0.06µg/mL, 0.03µg/mL and LOQ values were found to be 0.2µg/mL, 0.19µg/mL and 0.10µg/mL for Lamivudine, Abacavir and Dolutegravir respectively which were linear showing correlation coefficient of 0.999 in all the cases. Compounds which are eluted were detected by PDA detector at a wavelength of 257nm.

A chiral HPLC method was developed for the quantification of the Dolutegravir enantiomer and Dolutegravir diastereomer in Dolutegravir sodium drug substance by Chandra Shekara Reddy et al[14]. Both of this isomer are resolved on Lux cellulose-4, 250mm x 4.6mm, 5µ column using a mobile phase consisting of the mixture of acetonitrile, water and orthophosphorc acid in the ratio of 980:40:2 v/v/v. The mobile phase was pumped through the column at the flow rate of 1.5ml/min. The resolution between Dolutegravir enantiomer and Dolutegravir was found to be more than 3.0. The experimentally established limit of detection and quantification of Dolutegravir enantiomer is 0.006 and 0.018% w/w respectively and for Dolutegravir diastereomer are 0.007 and 0.21%w/w. The average percentage recovery of enantiomer was ranged between 10.28% and 1.302% and diastereomers was ranged between 97.5% and 96.2%. The linearity curve was found to be linear and correlation coefficient obtained was 0.9997 for enantiomer and 0.0003 for diastereomer.

Analytical method was developed by Devanna et al[15] for the simultaneous estimation of Lamivudine and Dolutegravir drug product by liquid chromatography. The chromatographic separation was achieved on C_{18} column at ambient temperature. The separation employing a mobile phase consists of 0.1% v/v TFA in water: ACN (30:70). The flow rate was 0.8ml/min and detected by using ultra violet detector at 260nm. The average retention time for Lamivudine and Dolutegravir was found to be 2.373 min and 4.558min. The assay method were found to be linear from 300-900 µg/ml for Lamivudine 50-150µg/ml for Dolutegravir.

A simple reliable analytical method was developed by Talari et al[16] to determine Dolutegravir sodium, Lamivudine and Tenofovir disoproxil fumarate in pharmaceutical effluents which are releasing into domestic water bodies by using RP- HPLC with UV absorption detector. The proposed method was quite reproducible and sensitive enough to detect the compounds at less than 10ppm level, which can replace the troublesome non-reproducible conventional analytical methods like UV-Visible spectrophotometric analysis or titrimetric analysis. The separation was achieved in C_{18} column using sodium dihydrogen phosphate with SDS as ion pair reagent having a pH of 2 as mobile phase A and acetonitrile and methanol as mobile phase B in gradient mode as mobile phase and at a flow rate of 1ml/min. Detection was carried out using a UV detector at 260nm. The total chromatographic analysis time per sample was about 30 min with Dolutegravir sodium, Lamivudine, Tenofovir disoproxil fumarate eluting at retention time of about 5.2min for Lamivudine, 11 min for Dolutegravir sodium and 13min for Tenofovir disoproxil fumarate. Linearity was observed for Dolutegravir sodium, Lamivudine and Tenofovir disoproxil fumarate in the concentration range of 0.05-7.5µg/ml (R2>0.95), the limit of detection and limit of quantitation was found to be 0.017µg/ml and 0.053µg/ml respectively for Dolutegravir,0.016µg/ml and 0.048µg/ml for lamivudine and 0.018µg/ml and 0.054µg/ml for tenofovir disoproxil fumerate. The RSD for the intraday and interday precision were found to be less than 5%.Factorial design for development of a high – performance thin- layer chromatography method for the simultaneous estimation of abacavir sulfate(ABC),lamivudine hydrochloride (LAM) and Dolutegravir sodium (DTG) has been performed by krupali dev et al. [22] A 23 full factorial design was utilized with pre-coated silica gel aluminium HPTLC plate 60f254 as the stationary phase and ethyl acetate -ethanol-acetone -ammonia (4.478:0.740:0.50:0.15v/v) as the mobile phase. Densitometric scanning was performed at a detection wavelength of 267nm.The effect of three factors like volume of ethylacetate, volume of ethanol, volume of acetone on the chromatographic response retardation factor(RF) on each drug has evaluated . The calibration curves were found to be linear by taking weighed standard solutions with concentration of 4.8,7.2,9.6,12.0 and 14.4mu;g per band for ABC,2.4, 3.6, 4.8, 6.0 and 7.2mu;g per band for LAM, and 0.4, 0.6, 0.8,1.0 and 1.2mu;g per band for DTG. In HPTLC method, analysis was carried out on aluminium-packed plates pre-

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coated with silica gel G60 F254 using methanol:chloroform:formic acid in the proportion of 8:2:0:5 v/v/v as the mobile phase. The solvent system found to produce compact spots with *Rf* value of 0.77±0.01. At 265nm, densitometric analysis of dolutegravir sodium was done.

Bioanalytical Techniques

Bioanalytical methods employed for the quantitative determination of drugs and their metabolites in biological matrix (plasma, urine, saliva, serum etc) play a significant role in evaluation and interpretation of bioavailability, bioequivalence and pharmacokinetic data. Both HPLC and LCMS-MS can be used for the bioanalysis of drugs in plasma.

Each of the instruments has its own merits. HPLC coupled with UV,PDA or fluroscence detector can be used for estimation of many compounds. The fundamental parameters for this validation include selectivity, accuracy, precision, linearity and range, limit of detection, recovery, robustness and stability.

Satyadev T.N,V,S.S et al[23] has illustrated High performance liquid chromatographic method for the determination of Dolutegravir in human plasma where he utilised hydrochlorothiazide as internal standard and mobile phase is of combination 20mm Sodium acetate (pH 4.0) and methanol. The flow is controlled at a rate of 1.0mL/min. Liquid-liquid extraction was carried out using methy-t-butyl ether and the internal standard were eluted under isocratic mode using a 150 ×4.6mm i.d, 5µm phenomenex ODS 2 C18 column, the detection was done at 254nm. The injection volume is 20µl. The run time of the method is 6 min with retention time 2.08 min and 4.16 for hydrochlorothiazide and Dolutegravir respectively. The method showed good linearity in the range of 101.90-7004.49ng/ml. The recovery of Dolutegravir is 59.21% with the coefficient of variation 3.72% and recovery of internal standard was 60.61% with a coefficient of variation 3.33%.

Development and validation of RP-HPLC for the estimation of dolutegravir and rilpivirine in bulk and pharmaceutical dosage and its application to rat plasma has done by Veeraswami et al[24] Separation was achieved on Phenomenex C1(150×4.6mm,5µm) Mobile phase composed of 0.1% Ortho phosphoric acid and acetonitrile in the ratio of 60:40 v/v at a flow rate of 1.0mL/min and the wavelength is set at 262nm.The method has shown a good linearity in the concentration range of 10 -15µg/ml for DTG and 5-75µG/ml for RPV under optimized conditions.

Chantelle Bennetto-Hood et al[25] has performed a sensitive HPLC-MS/MS method for the determination of Dolutegravir in human plasma. It is an assay method which required only a 20µL aliquot of human plasma subjected to acetonitrile protein precipitation utilizing stabled labelled isotope of DTG as internal standard. The technique was done with XBridge C18,2.1. ×50mm, reversed phase analytical column, mobile phase used is a mixture of acetonitrile and water in the ratio 60:40 containing 0.1% formic acid.

UPLC

Simultaneous estimation of lamivudine, abacavir, and dolutegravir in pure and tablet dosage forms by UPLC method has been demonstrated by Somshankar dubey et al[26]. Separation technique was carried out using Waters-ACQUITY UPLC system equipped with autosampler .The process was done with zodiac sil RP C18 (4.6mm - 250MM,3.0µm) column, phosphate buffer (pH 3.0) and methanol in the ratio of 30:70% v/v at a flow rate of 0.25 ml/min .The result was detected at a wavelength of 260nm with Ultraviolet detector. The mobile phase was used as a diluents. The retention time for lamivudine, abacavir and doultegravir were 1.763,2.247 and 3.175 min respectively. A good linear response was obtained in the range of 15- 75µg/mL,30-150 µg/mL and 2.5-12.5 µg/mL respectively. The Limit of detection values were found to be 0.021 µg/mL,0.330 µg/mL and 0.038 µg/mL, respectively and Limit of quantification values were 0.056 µg/mL,1.320 µg/mL and 0.095 µg/mL respectively.

Wang X et al[26] has illustrated a validated method for quantification of Dolutegravir using Ultra Performance Liquid Chromatography coupled with UV detection. It has utilised an analyte extraction from 100µL plasma. It was achieved by using a C8 reverse –phase analytical column using a gradient elution with 50mmol/L formic acid and 50 mmol/L ammonium acetate in water (mobile phase A),and 100% acetonitrile (mobile phase B) and the flow rate is set at 0.3 mL/min and the result was recorded wavelength at 258nm.The linearity of the calibration curve (r>0.9999,n=60 was validated over a concentration range of 0.25-10 mcg/mL. The overall accuracy ranged from 90.7% to 97.7% for the 3 different concentrations of quality control samples. Recovery efficiency of extraction ranged from 94.3- 100%.

CONCLUSION

Dolutegravir is an antiretroviral medication used together with other medication to treat HIV/AIDS. Antiretroviral therapy has lengthened the average life span of HIV-infected individuals to approach that of the general population while concurrently increasing the burden of comorbidities. Research shows that a combination or cocktail of drugs is the best way to control HIV and lower the chances that the virus become resistant to treatment. Huge reductions have been seen in rates of death and suffering when use is made of a potent ARV regimen, particularly in early stages of the diseases. In this review, we summarized analytical methods like UV, HPLC, HPTLC, UHPLC, bioanalytical techniques that can be used in the quantitative determination of Dolutegravir. Among which HPLC method was found to be most reliable and efficient technique for the routine analysis of antiretroviral drug.

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