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Development and validation of stability-indicating HPLC method for simeltaneous determination of Lamivudine, Tenofovir, and Dolutegravir in bulk and their tablet dosage form

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ABSTRACT

Objective: A Simple, accurate, specific and rugged reverse phase liquid chromatographic method was developed for the simultaneous estimation of Lamivudine, Tenofovir, and Dolutegravir in bulk and tablet dosage form.
Methods: A reverse phase gradient program has been developed to separate the all four active ingredients. The ingredients present in different concentrations and chromatographic behavior 0.05 M Phosphate buffer pH 6.2 ± 0.05 adjusted with dilute potassium hydroxide solution, Acetonitrile was used as mobile phase. A gradient programing has been done, on a reverse phase C18 column (250 × 4.6 mm, 5 micron) with a flow rate 1 mL/min, monitored at 260 nm.
Results: The mean retention times of Lamivudine, Tenofovir, and Dolutegravir were found to be 2.8, 5.2 and 11.5 min respectively. Linearity of Lamivudine, Tenofovir, and Dolutegravir was found to be 27 −162 μg/mL, 27−162 μg/mL and 4.5−28 μg/mL respectively.
Conclusion: The proposed method was validated in terms of Linearity, Range, Accuracy, Precision, Specificity, Robustness and stability studies and the method is successfully applies to the estimation of Lamivudine, Tenofovir, and Dolutegravir in combined tablet dosage form.
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1. Introduction

Lamivudine, chemically 4-amino-1-[(2R, 5S)-2-(hydroxyl methyl)-1, 3-oxathiolan-5-yl]-1, 2-dihydropyrimidin-2-one. Lamivudine is reverse transcriptase reported to be active against HIV-1, HIV-2 and hepatitis B virus. Lamivudine [Fig. 1] has been used for treatment of chronic hepatitis B at a lower dose than for treatment of HIV. It improves the seroconversion of e-antigen positive hepatitis B and also improves histology staging of the liver [1–3]. Tenofovir disproxil Fumarate is fumaric acid salt of the bis isopropoxy carbonyl oxy methyl ester derivative of Tenofovir [Fig. 2]. Chemically it is 9-[(R)-2- [[(isopropoxcarbonyl)-oxy] methoxy] phosphinyl] methoxy] propyl] adenine fumarate [4–7]. Dolutegravir (DTG, S/GSK-1349572, [Fig. 3] is a newly developed human immunodeficiency virus (HIV) integrase inhibitor from ViiV Healthcare (Research Triangle Park, NC, USA). DTG is an integrase strand transfer inhibitor (INSTI) that does not require ritonavir for cytochrome P450 3A4 inhibition, and preferentially blocks the strand transfer step of integration of the viral genome into the host cell's DNA [8], which is a two-step process mediated by the viral integrase enzyme. Like the other approved INSTIs raltegravir (RAL) and elvitegravir (EVG), DTG inhibits the binding of the integrase-viral DNA complex to host cell DNA by chelating $Mg2+$ ions in the active site [9]. Once integration is blocked, HIV-1 can no longer replicate, and the viral replication cycle is interrupted. In phase II trials, DTG has been shown to be highly effective at rapidly decreasing viral burden, with a concomitant increase in $CD4+$ cell count, in treatment-naïve patients receiving 10, 25 or 50 mg once-daily along with a nucleoside reverse transcriptase inhibitor (NRTI) background [10].

A variety of methods are in vogue for estimation of TDF, LMV and DTG individually as highlighted in the literature [11,12,13].

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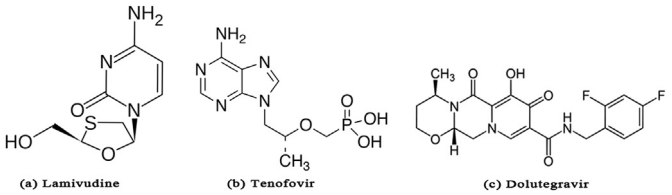

Fig. 1. Chemical structures of (a) Lamivudine (b) Tenofovir (c) Dolutegravir.

Literature survey reveals that Tenofovir disoproxil fumerate is estimated sensitive determination in plasma by HPLC [14], Plasma LC/MS/MS [15]and in human peripheral blood mononuclear cells methods [16], Similarly for Lamivudine estimation in human serum by HPLC [17–19], the simultaneous estimation of Lamivudine and Tenofovir disoproxil fumerate in RP- HPLC [20,21], HPTLC [22,23] and LC-MS/MS were reported.

To the best of our knowledge, there is no reported RP - HPLC method for simultaneous estimation of Lamivudine, Tenofovir and Dolutegravir in pharmaceutical formulations, previous to our work. Thus, efforts were made to develop fast, selective and sensitive analytical method for the estimation of Lamivudine, Tenofovir and Dolutegravir in their combined dosage form using reverse phase high performance liquid chromatographic method. In the current work author developed a simple, reliable and reproducible RP-HPLC method which was duly validated by statistical parameters precision, accuracy and recovery. The method has been satisfactorily applied to the simultaneous estimation of Lamivudine, Tenofovir and Dolutegravir in bulk and pharmaceutical dosage forms.

2. Experimental

2.1. Materials

The Pharmaceutical grade working standards of Lamivudine, Tenofovir, and Dolutegravir were obtained as a gift from Richer Pharmaceuticals (Prasanthinagar, Hyderabad, India). Fixed dosage combination tablet containing 300 mg Lamivudine, 300 mg Tenofovir, and 50 mg Dolutegravir was purchased from local market Hyderabad, India. All the chemicals were HPLC grade purchased from sd Fine Chem., Mumbai. MilliQ water was used.

2.2. Chromatographic conditions

Waters e 2695 series HPLC consisting pump, Auto sampler, Auto injector, VWD & photo diode array detector, thermostatic column

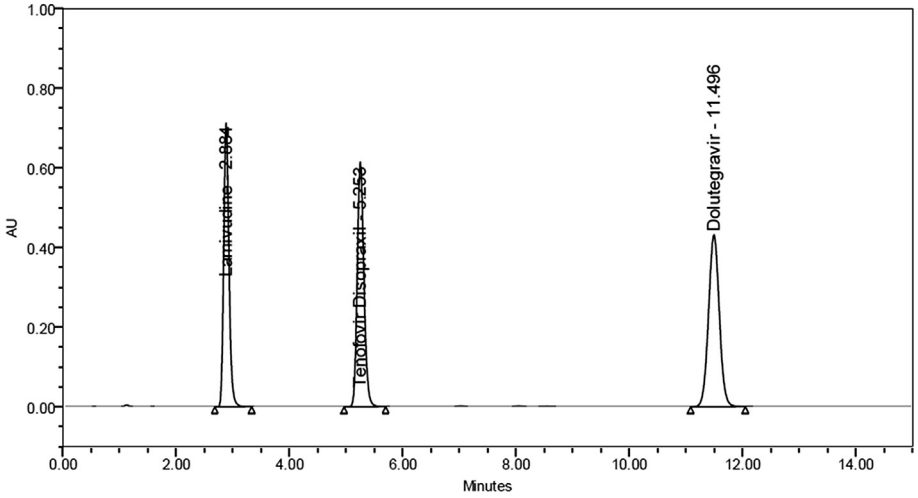

Fig. 2. System suitability chromatogram.

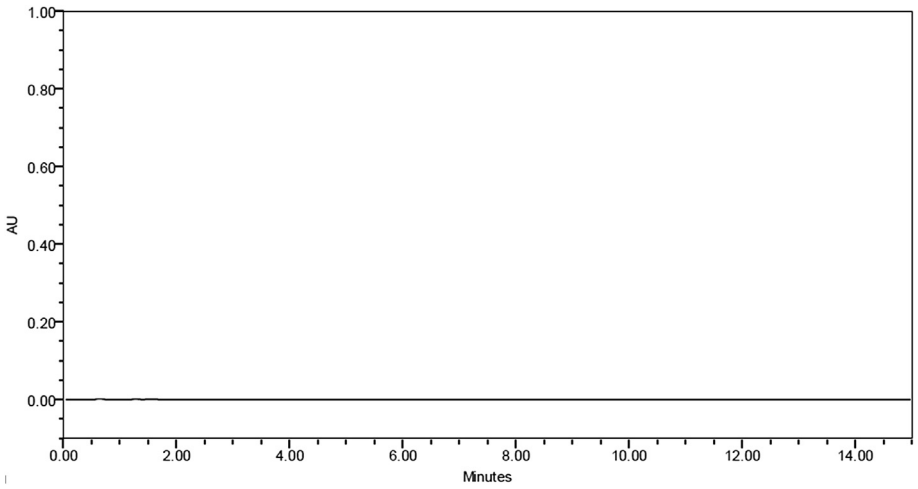

Fig. 3. Blank chromatogram.

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