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Development and Validation of RP-HPLC Method for Simultaneous Estimation of Dapagliflozin and Telmisartan in Synthetic Mixture

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KEYWORDS
Dapagliflozin; Telmisartan; RP-HPLC; Validation; Simultaneous Estimation

ABSTRACT:
The current's work objective is to propose and validate straight-forward and robust RP-HPLC method for concurrent determination of Dapagliflozin (DAP) and Telmisartan (TEL) in blend. A 150 × 4.6 mm, 5 µm Nucleosil ODS C18 Column was used for the separation, which was kept at 35 °C. Methanol and buffer (25:75% v/v) were used as the eluent, flowing at a rate of 1.0 mL/min with a detection wavelength of 224 nm. The injection volume was 40 µL. In compliance with ICH criteria, the analytical approach was successfully validated (ICH Q2 R1). Retention time for DAP and TEL were 4.78 and 7.77 min individually. DAP and TEL showed linear response from 5-15 µg/mL and TEL from 40 -120 µg/mL with correlation coefficient (r) as 0.9989 and 0.9988 individually. The outcomes of accuracy and precision were found within the acceptance range. Limit of Detection (LOD) is 1.33 and 10.87 µg/mL & Limit of Quantitation (LOQ) is 4.05 and 32.94 µg/mL for DAP and TEL, individually. The current approach was found precise, accurate, robust and could be beneficially utilized for the concurrent analysis of DAP and TEL in dosage form.

INTRODUCTION:

The occurrence of kidney dysfunction or a predicted glomerular filtration rate, or eGFR of below sixty milliliters per minute per 1.73 m^2 that lasts for three months or more is known as chronic kidney disease (CKD)[1]. It is estimated that 850 million people worldwide suffer from kidney disease, the majority of whom reside in low-income and lower-middle-income nations (LICs and LMICs), and many of them do not have access to screening, early detection, or medical care for renal disease [2]. DAP (Fig. 1(A)), sodium-glucose cotransporter 2 (SGLT2) inhibitor, found mostly in the tubule (proximal) of the nephron. Blocking it allows glucose to be excreted in the urine. This aids in weight loss and better blood sugar regulation for people with type 2 diabetes [3].While, TEL (Fig. 1(B)) selectively and reversibly binds to AT1 receptors in the adrenal gland and vascular smooth muscle. This blocks angiotensin II from attaching. As a result, systemic vascular resistance decreases [4]. According to a literature review, several RP-HPLC methods have been published for the determination of DAP in bulk and dosage form [3,5-13] and with other drugs also [14-17]. In the same manner, certain RP-HPLC methods were also reported for TEL estimation in alone [4, 18-27] and with other drugs [28-33]. The fixed-dose combination of DAP and TEL was recently approved by CDSCO for phase – 3 trial on 5 Dec 2023 [34]. Till date, there is no single RP-HPLC method was reported for the concurrent quantitation of DAP and TEL in formulation. Hence, the aim of current work is to create and validate precise, accurate and linear RP-HPLC method for concurrent quantitation of DAP and TEL in synthetic mixture. Validation of developed method is conducted as per ICH Q2 (R1) Guideline [35].

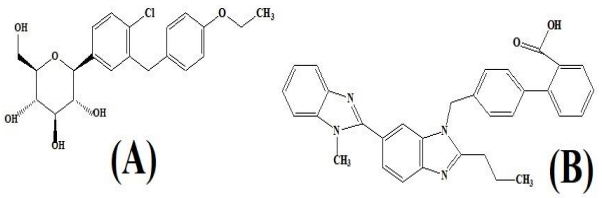

Fig. 1: Structure of (A) DAP and (B) TEL

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MATERIALS AND METHODS:

Chemical and Reagents:

DAP and TEL were gifted from 4 care Lifescience Pvt. Ltd, Bagdol (Kathlal), Gujarat and Zydus Lifescience Ltd, Ahmedabad, Gujarat individually. Milli-Q Water, Methanol (MeOH), Acetonitrile (ACN) and Potassium dihydrogen phosphate (KH_2PO_4) of HPLC Grade were bought from Merck Lifescience Pvt. Ltd. The excipients required for synthetic mixture were bought from S. D. Fine Chemicals Ltd, Mumbai.

Instrument and Experimental Conditions:

A Shimadzu HPLC (LC 2010 CHT) equipped with detector (UV) was utilised for the analysis. Nucleosil ODS-A C18 Column (150 × 4.6 mm, 5µm) was the analytical column employed for the separation. LC solution software was utilized for data interpretation. 35°C was set as column temperature. A mixture of 20mM KH_2PO_4 Buffer and Methanol (25:75 % v/v) was finalized as eluent. A flow rate of 1.0 mL/min was used. The wavelength of the detector was 224 nm. The injection volume was 40 µL.

Solutions Preparation:

Buffer Solution Preparation (20 mM Phosphate Buffer):

After being weighed, 2.72 g of potassium dihydrogen phosphate (KH2PO4) was added to one liter of water, and then sonicated for 10 min. Using ortho-phosphoric acid, pH was adjusted to 4.5.

Preparation of Mobile Phase:

Buffer (25 volumes) and methanol (75 volumes) were combined to prepare 1 L Mobile Phase and degassed using a sonicator, then vacuum-filtered through 0.45-micron membrane filter. It was utilized as diluent.

Preparation of Stock Solution of DAP (100 µg/mL) and TEL (800 µg/mL):

10 mg of DAP and 80 mg of TEL were precisely weighed and kept in 100 mL volumetric flask (VF), individually. 20 mL MeOH was poured in both VF and then kept in sonicator for 15 min to dissolve the contents. Rest of the volume was diluted with MeOH.

Mixed Standard Solution Preparation:

1 mL each of the DAP and TEL stock solution were taken into a 10 mL VF. Add the diluent up to the mark to prepare the mixed standard solution.

Synthetic Mixture Preparation:

The blend was formulated by combining 10 mg DAP and 80 mg TEL with routinely utilized excipients like MCC pH 101, HPC, Magnesium stearate, Cross Povidone, Talc and Sorbitol as for one Tablet. After precisely weighing the synthetic mix powder, which is equal to one tablet (around 300 mg), was put into a 100 mL VF with 20 mL of MeOH. After that, VF was subjected to sonication for 15 min to mix the contents. The mixture was made up to the mark with the diluent, with intermittent shaking to ensure thorough mixing. The resultant solution was filtered using a 0.45 µm filter. After transferring, 1 mL of filtrate into a 10 mL VF, the diluent was added gradually until the final concentration of 10 µg/mL DAP and 80 µg/mL TEL were achieved.

Analytical Method Validation:

The current approach was validated as ICH guidelines Q2 (R1)[35],which include parameters such as linearity, system suitability, precision, limit of detection (LOD), specificity, robustness, accuracy, and limit of quantification (LOQ). To ensure the system's suitability, 40 µL of each standard solution (working) of DAP (10 µg/mL) and TEL (80 µg/mL) were injected into the HPLC system six times (n=6). The % RSD was determined after recording the retention time (Rt), theoretical plates (TP), resolution (Rs), and tailing factor (Tf). Specificity was carried out by injecting blank, placebo, standard as well as sample to study the interference of excipients and the analytes. Chromatograms were recorded and retention time for blank, placebo, standard and sample were compared for identification of analytes. The calibration standards were prepared across 5-15 µg/mL for DAP and 40-120 µg/mL for TEL. DAP and TEL stock solutions (0.5 0.75, 1, 1.25, and 1.5 mL) were added into set of 10 mL flasks individually and diluted with diluent. The calibration curve of peak area vs. concentration was used to find the R^2, slope, and Y-intercept. The precision of the current approach was carried out using repeatability, within-day and between-day studies. In repeatability, 6 determinations using the full (100 %) test concentration

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was carried out. In within-day precision three concentration of DAP (5, 10, 15 µg/mL) and TEL (40, 80, 120 µg/mL) were examined on the same day. While in between-days precision, three concentration of DAP (5, 10, 15 µg/mL) and TEL (40, 80, 120 µg/mL) were examined on 3 consecutive days. Then, the % RSD was calculated. The approach's accuracy was assessed employing placebo recovery method. Fixed amount (0.210 g) placebo was weighed and standard was spiked at 50 %, 100 %, and 150 %. Utilizing dilutions, final concentration of 5, 10, 15 µg/mL DAP and 40, 80, 120 µg/mL TEL were achieved. The mean slope and standard deviation of the Y-intercepts were used to determine the LOD and LOQ for DAP and TEL. The Robustness was carried out three times (n=3) by changing various factors like temperature (± 5 °C), flow rate (± 0.1 mL/min), pH (± 0.2), composition of organic ratio (± 2 %) and wavelength (± 2 nm). The stability of DAP and TEL solutions was tested by storing the sample and standard solutions separately in volumetric flasks with tightly sealed caps for 24 h at room temperature. The solution was examined periodically over 6 to 24 h.

RESULTS AND DISCUSSION:

The goal of this work was to create a quick and precise technique for RP-HPLC DAP and TEL quantitation. To optimize the chromatographic condition for the concurrent assessment of DAP and TEL, trials were made as per literature review and physicochemical properties of both drugs including different columns (Inertsil ODS – 3 C18 (100 × 4.6 mm, 5µm) and Nucleosil ODS-A C18 Column (150 mm × 4.6 mm, 5µm)), different eluents in different ratios, variations in instrument parameters (FR, temperature). The column Nucleosil ODS-A C18 Column (150 mm × 4.6 mm, 5µm) was chosen during technique optimization based on the retention period, tailing factor, number of theoretical plates, and peak shape. Different combinations of eluents were tried like during the use of Water & MeOH in different ratios, no peak was observed. Then organic phase was changed to ACN, but only one peak was observed when the ratio of ACN was increased to 90 % and when its amount is decreased, one peak was eluted in dead volume. Then, Buffer and MeOH was also tried in different proportions,(as it provide the ideal polarity for peak migration and resolution) but better results were obtained using a mobile phase of 20mM KH_2PO_4 Buffer and Methanol (25:75 % v/v) which exhibited sharp peaks for DAP and TEL at a retention time of 4.78 and 7.77 min respectively (Figure 1). The separation was achieved at 35 ºC at a flow rate of 1.0 mL/min. Both of the drugs showed iso absorptive point at 224 nm (Figure 2), hence it was selected for detection.

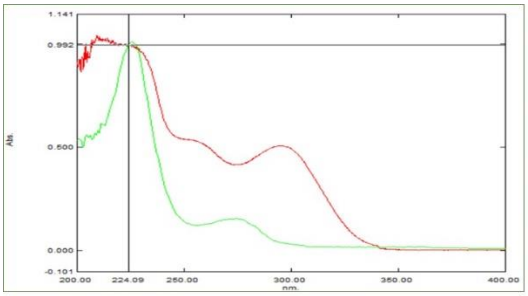

Fig. 2: Overlain UV spectra of DAP (10 µg/mL) and TEL (10 µg/mL)

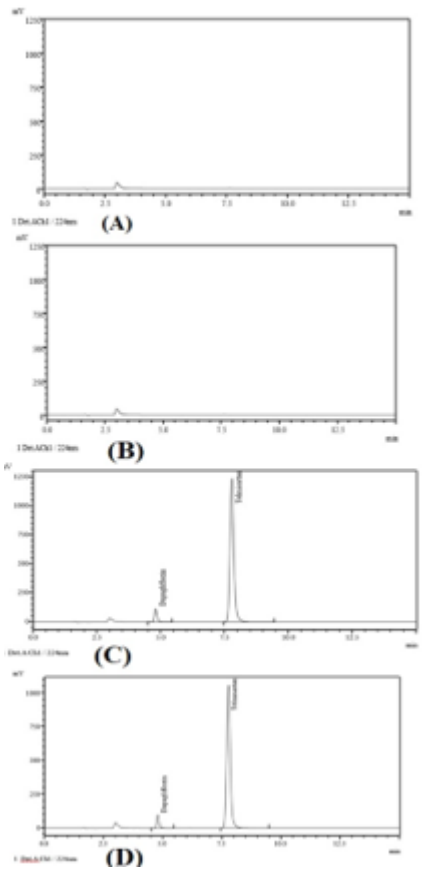

Fig. 3: HPLC Chromatogram of (A) Diluent, (B) Placebo, (C) Standard solution of DAP (10 µg/mL) and TEL (80 µg/mL), (D) Sample solution of DAP (10 µg/mL) and TEL (80 µg/mL)

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Method Validation:

The proposed technique was validated by ICH Q2 (R1), which include parameters such as linearity, precision, LOD, LOQ, accuracy and robustness. All the System suitability parameters (Rt, N, Tf, and Rs) fell within the acceptance range. The results were presented in Table 1. The chromatograms of standard, blank, sample and placebo were shown in Figure 3. It was confirmed, that no more peaks seen at both drug's Rt and the current approach was specific for the concurrent quantitation of both drugs in laboratory prepared mixture. To assess linearity, the approach shows a straight-line response for concentrations between 5 - 15 µg/mL, with a correlation coefficient value R^2 = 0.9989 for DAP and the 40 – 120 µg/mL level range, with a correlation coefficient of R^2 = 0.9988 for TEL. The % RSD of DAP and TEL for repeatability were 1.08 and 0.74 correspondingly. The outcomes for intermediate precision study for DAP and TEL indicate that the % RSD results were within limits. The method was accurate because % recovery fell within expected range from 99.7 – 101.6 % for DAP and 99.3 % - 99.8 % for TEL, respectively. The results were presented in Table 2. The LOD is 1.33 and 10.87 µg/mL & LOQ is 4.05 and 32.94 µg/mL for DAP and TEL, correspondingly. The % RSD for the DAP and TEL peak areas was less than 2%, indicating that the approach is robust. The outcomes were mentioned in Table 2. An analysis of a synthetic mixture was used to determine the applicability of the suggested approach. The average findings were 98.65 % ± 0.450 and 101.0 % ± 0.900 for DAP and TEL respectively. The solution of DAP and TEL was found stable for one day as % assay difference was stated less than 2 %.

Table 1: Outcomes of System Suitability

Limit (n = 6)	DAP (Average ± SD), % CV	TEL (Average ± SD), % CV
R_t	4.851 ± 0.007, 0.16	7.91 ± 0.014, 0.18
TP	10170.2 ± 65.021, 0.63	11672.4 ± 31.007, 0.26
T_f	1.36 ± 0.004, 0.29	1.14 ± 0.008, 0.69
R_s	--	12.5 ± 0.074, 0.59

Table 2. Summary of Validation Parameters

Sr. No.	Parameter		DAP	TEL
1	Specificity		No interference	No interference
2	Range for linearity (µg/ml)*		5 - 15	40 - 120
3	Equation of Regression		y = 61514x + 3013.1	y = 124826x + 49148
4	Coefficient of determination (R^2)		0.9989	0.9988
5	Precision (% RSD)	Repeatability#	1.08	0.74
		Within - day*	0.24-1.11	0.03-0.94
		Between day*	0.53-1.20	0.04-0.77
6	Accuracy (% recovery)*		99.7-101.6	99.3-99.8
7	Robustness (% RSD)	Change in DL (± 2 nm)*	(+) 0.71, (-) 0.43	(+) 0.86, (-) 0.66
		Change in FR (± 1 mL/min)*	(+) 0.53, (-) 0.65	(+) 0.32, (-) 0.96
		Change in Column Temperature (± 5 ºC)*	(+) 0.66, (-) 0.93	(+) 0.66, (-) 0.89
		Change in pH (± 0.2)*	(+) 0.70, (-) 0.51	(+) 0.45, (-) 0.42

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		Change in composition of organic phase (± 2 %)*	(+) 0.78, (-) 0.41	(+) 0.22, (-) 0.62

CONCLUSION:

The study of quantitation of DAP and TEL in a synthetic mixture has been achieved through the development and validation of a novel, simple, reliable, and precise RP-HPLC technique. All validation parameters including specificity, linearity, accuracy, precision, LOD, LOQ and robustness were performed and determined to be within acceptable limits. For all parameters, the % RSD values were less than 2 %, indicating that the outcomes obtained by this methodology are in good accord. As a result, this reverse-phase high performance liquid chromatography approach may be used for regular QC assessing of DAP and TEL in formulation. This approach can be further utilised for the stress degradation study of DAP and TEL under various stimuli.

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CONFLICT OF INTEREST:

None to declare.

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