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Development and Validation of RP-HPLC Method for Simultaneous Estimation of Tezacaftor and Ivacaftor in Bulk and Pharmaceutical Dosage Forms

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ABSTRACT
A rapid and precise Reverse-Phase High Performance Liquid Chromatographic (RP-HPLC) method has been developed and validated for tezacaftor and ivacaftor, in its pure form as well as in tablet dosage form. Chromatography was carried out on an Altima C18 (4.6 x 150mm, 5µm) column using a mixture of acetonitrile, methanol and phosphate buffer pH 4.6 (10:25:65 v/v) as the mobile phase at a flow rate of 1.0ml/min, the detection was carried out at 234nm. The retention time of the ivacaftor and tezacaftor was 2.088, 6.068±0.02min respectively. The method produces linear responses in the concentration range of 25-125ppm of ivacaftor and 10-50ppm of tezacaftor. The method precision for the determination of assay was below 2.0 %RSD. The method is useful in the quality control of bulk and pharmaceutical formulations. Hence the proposed RP-HPLC method can be used in routine analysis of drugs in bulk as well as in tablets containing ivacaftor and tezacaftor.
Key words: *Ivacaftor, tezacaftor, RP-HPLC, validation, linearity, CFTR potentiator.*

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INTRODUCTION

Ivacaftor is chemically N-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. Ivacaftor is in a class of medications called cystic fibrosis transmembrane conductance regulator (CFTR) potentiators. Ivacaftor exerts its effect by acting as a potentiator of the CFTR protein, an ion channel involved in the transport of chloride and sodium ions across cell membranes of the lungs, pancreas, and other organs [1-3].

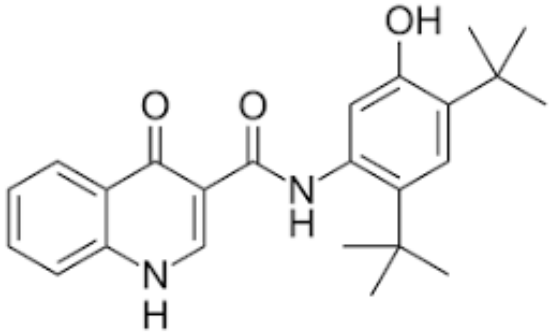

Figure 1: Ivacaftor structure

Tezacaftor is chemically named as, 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-[1-[(2R)-2,3-dihydroxy propyl]-6-fluoro-2-(1-hydroxy-2-methyl propan-2-yl)indol-5-yl] cyclopropane carboxamide. Tezacaftor is a drug of the cystic fibrosis transmembrane conductance regulator (CFTR) potentiator class. It functions as a corrector to facilitate the folding and presentation of the mature CFTR protein to the cell surface, improving CFTR function [4-6].

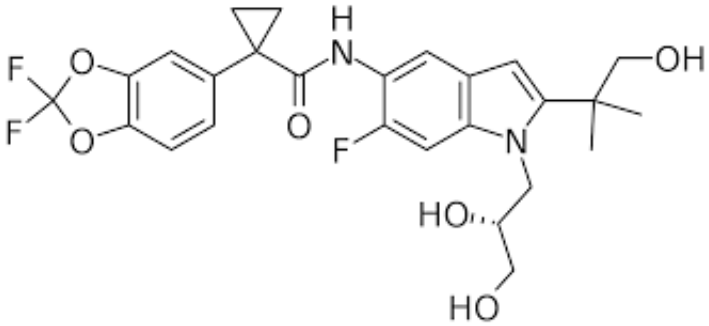

Figure 2: Tezacaftor structure

From the literature survey, it was revealed that there are many analytical methods for the estimation of ivacaftor and tezacaftor in single and in combination form [7-9], but till now there is no simple and accurate method. Thus, the present study is mainly focussed to develop an accurate, precise, sensitive, selective, reproducible and rapid analytical technique for cost effective simultaneous estimation of tezacaftor and ivacaftor.

MATERIAL AND METHODS

Materials

The standard drug ivacaftor (API) and tezacaftor (API) was a gift sample obtained from Sura Labs, Hyderabad, Telangana. The chemicals water and methanol (Merck), acetonitrile (Merck) used for mobile phase preparation and dilutions were of HPLC grade.

Instruments used

The present work was carried on a Waters HPLC [WATERS Alliance 2695 separation module, software: Empower 2, 996 PDA Detector] instrument which is equipped with Empower 2 software for data processing. The optimization and separation of the drugs were achieved on Altima C18 (4.6×150mm, 5µ) analytical column. The eluate was detected at 234nm using 996 Photo-diode array detectors. Dissolution and degassing of the prepared solutions were achieved on an Labman digital ultrasonicator. The pH of the buffer solution was adjusted using a Lab India pH meter.

Experimental work

Preparation of buffer and mobile phase [10-14]

Preparation of Phosphate buffer (pH-4.6): Dissolved 0.9g of anhydrous di-hydrogen phosphate and 1.298 g of citric acid mono hydrate in sufficient water to produce 1000mL. Adjusted the pH to 4.6 by using ortho phosphoric acid.

Preparation of mobile phase: Accurately measured 650 ml (65%) of buffer and 250ml of methanol (25%) and 100ml (10%) of acetonitrile were mixed and degassed in digital ultrasonicator for 10min and then filtered through 0.45µ filter under vacuum filtration.

HPLC method development15-18

Preparation of standard solution: Accurately weighed and transferred 10mg of ivacaftor and tezacaftor into a 10ml of clean dry volumetric flasks added about 7ml of mobile phase and sonicated to dissolve and for removal of air completely and make volume up to the mark with the same mobile phase. Further pipetted 0.375ml of ivacaftor and 0.3ml of the tezacaftor from the above stock solutions into a 10ml volumetric flask and diluted up to the mark with diluents.

Procedure: Injected the samples by changing the chromatographic conditions and recorded the chromatograms, noted the conditions of proper peak elution for performing validation parameters as per ICH guidelines.

Mobile phase optimization: Initially the mobile phase tried was methanol: orthophosphoric acid and phosphoric acid (pH 3):acetonitrile and methanol:acetonitrile (ACN) with varying proportions. Finally, the mobile phase was optimized to buffer:methanol:ACN in proportion 65:25:10v/v respectively.

Optimization of column: The method was performed with various columns like C18 column, ODS and Zodiac column. Altima C18 (4.6×150mm, 5µ) was found to be ideal as it gave good peak shape and resolution at 1ml/min flow. After all the trials, the achieved optimized method was finalized and proceeded to carry out method validation.

Method validation19-20

Method validation was proceeded by using various analytical parameters like accuracy, precision, linearity, detection limit, quantitation limit and robustness based on guidelines given by ICH10-12.

System suitability

For checking the ability of the complete system or reagents used, system by injecting the standard solution for five times and measured the peak area for all five injections in HPLC. The %RSD for the area of five replicate injections was calculated.

Specificity study of drug

Preparation of sample solution: Taken an average weight of tablet and crushed in a clean and dry mortar by using pestle and weighed 10mg equivalent weight of ivacaftor and tezacaftor sample into a 10mL clean and dry volumetric flask and added about 7mL of diluent and sonicated to dissolve it completely and make volume up to the mark with the diluent. Further pipetted 0.375ml of ivacaftor and 0.3ml of the tezacaftor from the above stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.

Procedure: Injected the three replicate injections of standard and sample solutions and calculated the assay by using formula:

$$\%Assay = \frac{\text{Sample area}}{\text{Standard area}} X \frac{\text{Wt.of standard}}{\text{Dilution of standard}} X \frac{\text{Dilution of sample}}{\text{Wt.of sample}} X \frac{\text{Purity}}{100} X \frac{\text{Wt.of tablet}}{\text{Label claim}} X100$$

Linearity

Preparation of drug solutions for linearity

Preparation of level – I (12.5ppm of ivacaftor &10ppm of tezacaftor): Pipetted out 0.125ml of ivacaftor and 0.1ml of tezacaftor stock solutions into a 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of level – II (25ppm of ivacaftor & 20ppm of tezacaftor): Pipetted out 0.25ml of ivacaftor and 0.2ml of tezacaftor stock solutions into a 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of level – III (37.5ppm of ivacaftor & 30ppm of tezacaftor): Pipetted out 0.375ml of ivacaftor and 0.3ml of tezacaftor stock solutions into a 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of level – IV (50ppm of ivacaftor & 40ppm of tezacaftor): Pipetted out 0.5ml of ivacaftor and 0.4ml of tezacaftor stock solutions into a 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of level – V (62.5ppm of ivacaftor & 50ppm of tezacaftor): Pipetted out 0.625ml of ivacaftor and 0.5ml of tezacaftor stock solutions into a 10ml of volumetric flask diluted up to the mark with diluent.

Procedure: Injected each level into the chromatographic system and measured the peak area. Plotted a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

Precision

Repeatability

Preparation of ivacaftor and tezacaftor product solution for precision: The standard solution was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

Intermediate precision: To evaluate the intermediate precision (also known as Ruggedness) of the method, precision was performed on different days by maintaining same conditions.

Procedure:

Day 1: The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Day 2: The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Accuracy

Preparation of 50% standard stock solution: Accurately weigh and transfer 10 mg of ivacaftor and 10mg of tezacaftor working standard into a 10ml of clean dry volumetric flasks add about 7mL of diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent (stock solution). Further pipetted 0.187ml of ivacaftor and 0.15ml of the tezacaftor from the above stock solutions into a 10ml volumetric flask and diluted up to the mark with diluents.

Preparation of 100% standard stock solution: Further pipetted 0.375ml of ivacaftor and 0.3ml of the tezacaftor from the above stock solutions into a 10ml volumetric flask and diluted up to the mark with diluents.

Preparation of 150% standard stock solution: Further pipetted 0.562ml of ivacaftor and 0.45ml of the tezacaftor from the above stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.

Procedure: Injected the three replicate injections of individual concentrations (50%, 100%, 150%) were made under the optimized conditions. Recorded the chromatograms and measured the peak responses. Calculated the amount found and amount added for ivacaftor and tezacaftor and calculated the individual recovery and mean recovery values.

Robustness

The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results.

Preparation of standard solution: Accurately weigh and transfer 10mg of ivacaftor and 10mg of tezacaftor working standard into a 10ml of clean dry volumetric flasks add about 7mL of diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent (stock solution). Further pipette 0.375ml of ivacaftor and 0.3ml of tezacaftor from the above stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.

Effect of variation of flow conditions: The sample was analyzed at 0.9ml/min and 1.1ml/min instead of 1ml/min, remaining conditions are same. 10µl of the above sample was injected and chromatograms were recorded.

Effect of variation of mobile phase organic composition: The sample was analyzed by variation of mobile phase i.e., buffer: methanol: ACN was taken in the ratio and 75:15:10, 55:35:10 instead 65:25:10, remaining conditions are same. 10µl of the above sample was injected and chromatograms were recorded.

RESULTS AND DISCUSSION

HPLC method development:

Table 1: Optimized chromatogram (standard)

Mobile phase	Buffer:methanol:ACN (65:25:10v/v)
Column	Altima C18 (4.6×150mm, 5.0 µm)
Flow rate	1ml/min
Wavelength	234nm
Column temperature	35ºC
Injection volume	10µl
Run time	14min

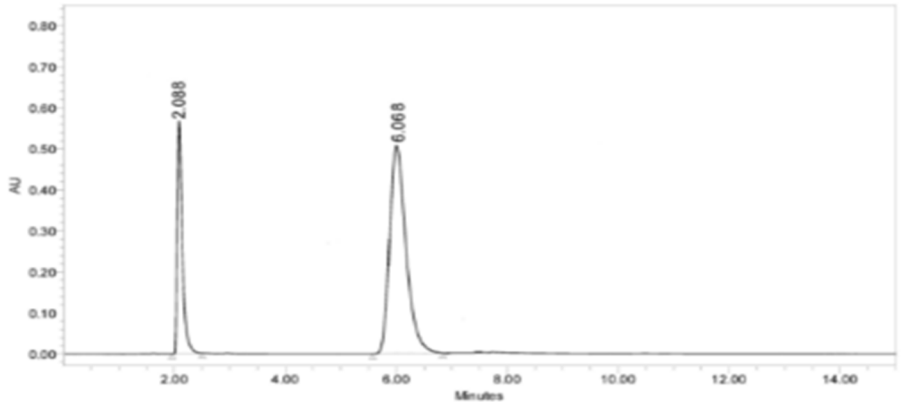

Figure 3: Optimized chromatogram

From the above chromatogram it was observed that the ivacaftor and tezacaftor peaks are well separated and all the efficiency parameters like retention time, resolution, peak tailing and theoretical plate count are found to be within the acceptance criteria. So, it is accepted as an optimized method and proceeded for Method validation as per ICH guidelines.

Table 2: Optimized chromatographic conditions

Peak name	Rt	Area	Height	USP resolution	USP tailing	USP plate count
Ivacaftor	2.088	3425413	567933		1.0	5565.5
Tezacaftor	6.068	1629854	517733	25	1.1	5355.2

Method validation

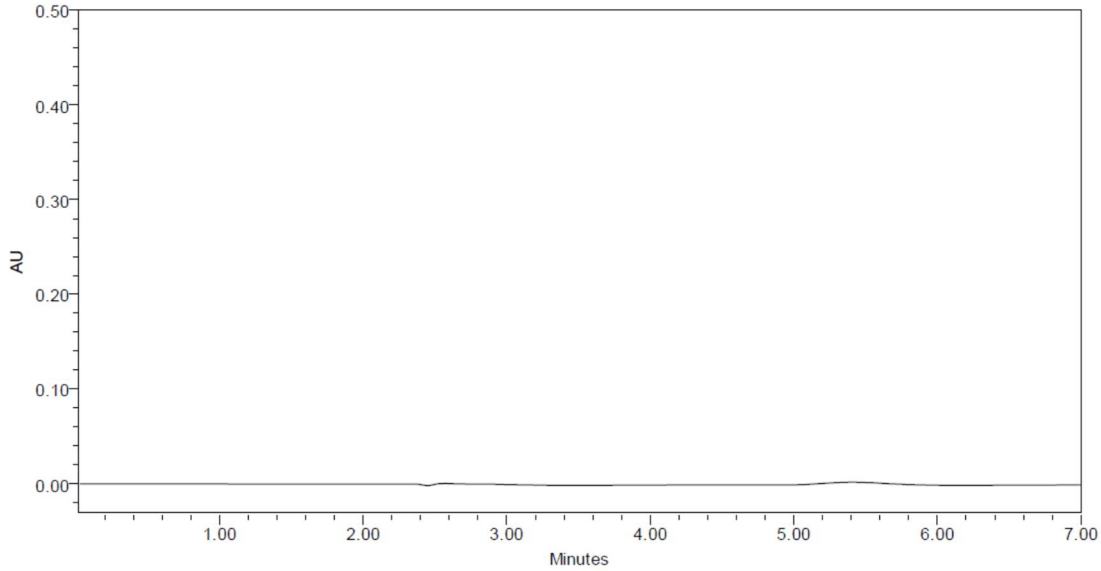

Figure 4: Chromatogram showing blank (mobile phase preparation)

System suitability

Table 3: Results of system suitability for ivacaftor

S. No.	Rt	Peak area	Peak height	USP plate count	USP tailing
1	2.080	3569412	567917	5568.0	1.0
2	2.080	3465125	517719	6359.2	1.1
3	2.080	3598154	567933	5565.5	1.0
4	2.081	3586491	517733	5355.2	1.1
5	2.081	3582694	567917	6348.0	1.0
Mean		3560375			
Std. Dev.		54225.61			
%RSD		1.523031			

Table 4: Results of method precision for tezacaftor

S. No.	Rt	Peak Area	Peak height	USP plate count	USP Tailing
1	2.080	3582264	567917	5568.0	1.0
2	2.080	3586491	517719	5359.2	1.1
3	2.080	3598154	567933	5565.5	1.0
4	2.081	3564125	517733	5355.2	1.1
5	2.081	3569412	562173	5568.0	1.0
Mean		3580089			
Std. Dev.		13609.81			
% RSD		0.380153			

Specificity

The ICH guidelines defined specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components. Analytical method was tested for specificity to measure accurately quantitate ivacaftor and tezacaftor in drug product.

Assay (standard):

Table 5: Peak results for assay standard

S. No.	Rt	Peak area	Peak height	USP resolution	USP tailing	USP plate count
1	2.087	3465681	567917		1.0	5568.0
2	6.067	16235984	517719	2.5	1.1	5359.2
3	2.088	3465413	567933		1.0	5565.5
4	6.068	16298543	517733	2.5	1.1	5355.2
5	2.088	3465423	567933		1.0	5545.5
6	6.068	16265213	517733	2.5	1.1	5352.1

Assay (sample):

Table 6: Peak results for assay sample

S. No.	Rt	Area	Height	USP resolution	USP tailing	USP plate count
1	2.089	3469821	567917		1.0	6568.0
2	6.069	16259845	517719	2.5	1.1	5359.2
3	2.090	3468547	567933		1.0	5565.5
4	6.070	16287531	517733	2.5	1.1	5355.2
5	2.090	3468143	567813		1.0	5391.1
6	6.070	16282431	517623	2.5	1.1	5564.0

The % purity of ivacaftor and tezacaftor in pharmaceutical dosage form was found to be 99.6%.

Linearity

Table 7: Linearity study data for ivacaftor

Concentration level (%)	Concentration (µg/ml)	Average peak area
33.3	25	1010252
66.6	50	2049374
100	75	3072706
133.3	100	3921068
166.6	125	4952813

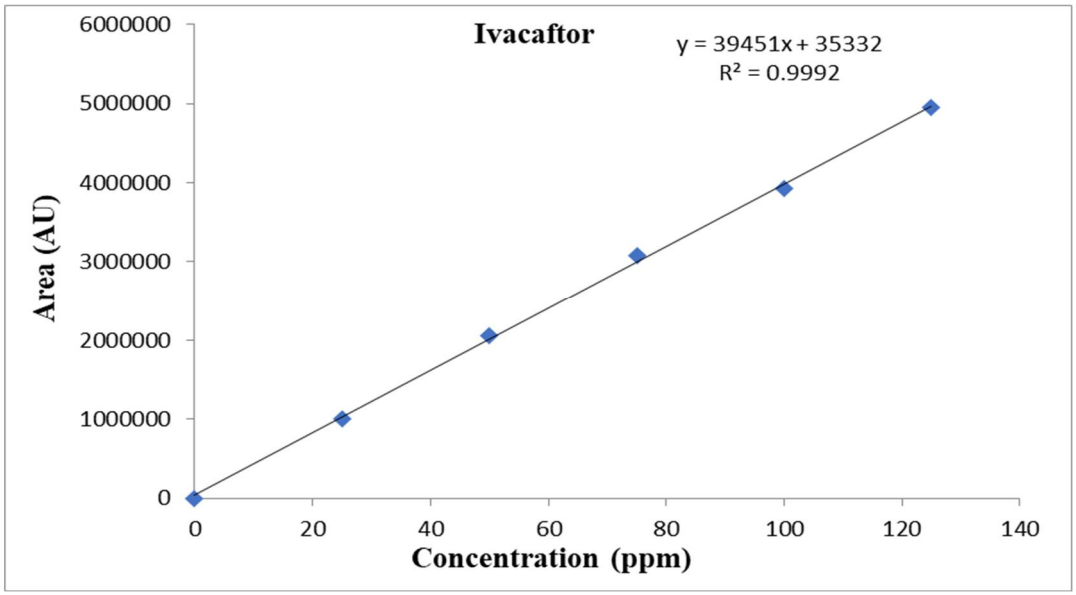

Figure 5: Calibration graph for ivacaftor

Table 8: Linearity study data for tezacaftor

Concentration level (%)	Concentration (µg/ml)	Average peak area
33	10	8040807
66	20	14318417
100	30	21087985
133	40	27913928
166	50	34584741

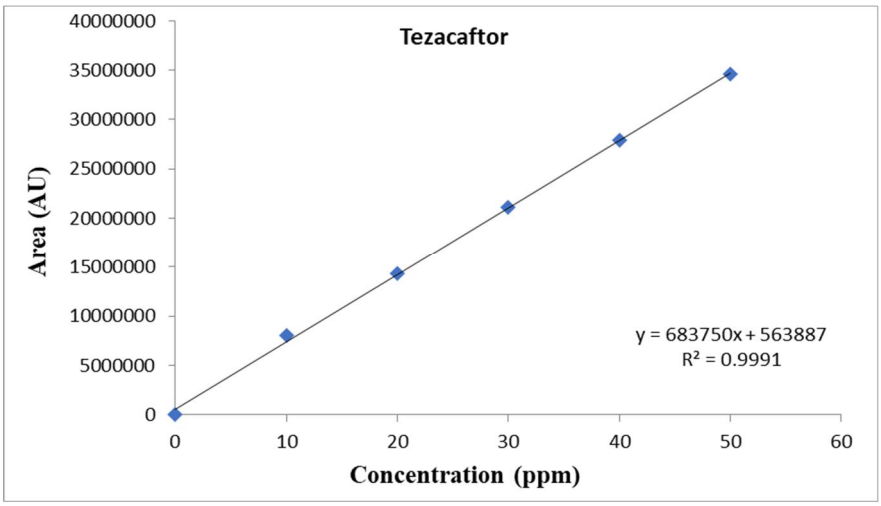

Figure 6: Calibration graph for Tezacaftor

Precision

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Repeatability

Obtained 5 replicates of 100% accuracy solution as per experimental conditions. Recorded the peak areas and calculated % RSD.

Table 9: Results of repeatability for ivacaftor

S. No.	Rt	Area	Height	USP plate count	USP tailing
1	2.084	3569412	567917	5568.0	1.0
2	2.083	3465125	517719	5359.2	1.1
3	2.082	3598154	567933	5565.5	1.0
4	2.081	3586491	517733	5355.2	1.1
5	2.080	3582694	567917	5568.0	1.0
Mean		3560375			
Std. Dev.		54225.61			
% RSD		1.523031			

Table 10: Results of method precision for tezacaftor

S. No.	Rt	Peak area	Height	USP plate count	USP tailing	USP resolution
1	6.056	1582264	567917	5568.0	1.0	2.5
2	6.057	1586491	517719	5359.2	1.1	2.5
3	6.058	1598154	567933	5565.5	1.0	2.5
4	6.059	1564125	517733	5355.2	1.1	2.5
5	6.060	1569412	562173	5568.0	1.0	2.5
Mean		1580089				
Std. Dev.		13609.81				
% RSD		0.861332				

Intermediate precision (Day 1):

Table 11: Intermediate precision for ivacaftor

S. No.	Rt	Area	Height	USP plate count	USP tailing
1	2.081	3481579	567917	5568.0	1.0
2	2.082	3458121	517719	5359.2	1.1
3	2.083	3426581	567933	5565.5	1.0
4	2.084	3465712	517733	5355.2	1.1
5	2.085	3451476	567917	5568.0	1.0
6	2.085	3452106	567514	5359.2	1.1
Mean		3455929			
Std. Dev.		18188.92			
% RSD		0.5			

Table 12: Intermediate precision for tezacaftor

S. No.	Rt	Area	Height	USP plate count	USP tailing	USP resolution
1	6.061	15481579	567917	5568.0	1.0	2.5
2	6.062	15369852	517719	5359.2	1.1	2.5
3	6.063	15248454	567933	5565.5	1.0	2.5
4	6.064	15874692	517733	5355.2	1.1	2.5
5	6.064	15236547	567933	5568.0	1.0	2.5
6	6.064	15217547	567133	5359.2	1.1	2.5
Mean		15404779				
Std. Dev		251289.4				
% RSD		1.6				

Table 13: Intermediate precision day 2 for ivacaftor

S. No.	Rt	Area	Height	USP plate count	USP tailing
1	2.081	3481579	567917	5568.0	1.0
2	2.082	3458121	517719	5359.2	1.1
3	2.083	3426581	567933	5565.5	1.0
4	2.084	3465712	517733	5355.2	1.1
5	2.085	3451476	567917	5568.0	1.0
6	2.085	3452106	567514	5359.2	1.1
Mean		3455929			
Std. Dev.		18188.92			
% RSD		0.5			

Table 14: Intermediate precision for tezacaftor

S. No.	Rt	Area	Height	USP plate count	USP tailing	USP resolution
1	6.061	15481579	567917	5568.0	1.0	2.5
2	6.062	15369852	517719	5359.2	1.1	2.5
3	6.063	15248454	567933	5565.5	1.0	2.5
4	6.064	15874692	517733	5355.2	1.1	2.5
5	6.064	15236547	567933	5568.0	1.0	2.5
6	6.064	15217547	567133	5359.2	1.1	2.5
Mean		15404779				
Std. Dev.		251289.4				
% RSD		1.6				

Accuracy

Accuracy at different concentrations (50%, 100%, and 150%) were prepared and the % recovery was calculated.

Table 15: The accuracy results for ivacaftor

%Concentration (at specification level)	Area	Amount added (ppm)	Amount found (ppm)	% Recovery	Mean recovery
50%	1543793	37.5	37.52	101.9	**100.9%**
100%	3035883	75	75.1	101.4	
150%	4451005	112.5	112.47	99.4	

Table 16: The accuracy results for tezacaftor

%Concentration (at specification level)	Area	Amount added (ppm)	Amount found (ppm)	% Recovery	Mean recovery
50%	1084420	15	15.07	100.2	**99.6%**
100%	2096069	30	29.6	99.4	
150%	3112684	45	44.8	99.5	

LOD and LOQ

$$\mathbf{LOD = 3.3 \times \sigma / s}$$

Where, σ = Standard deviation of the response,

S = Slope of the calibration curve.

$$\mathbf{LOQ = 10 \times \sigma / S}$$

Where, σ = Standard deviation of the response,

S = Slope of the calibration curve.

Table 17: LOD and LOQ

Drug	LOD	LOQ
Ivacaftor	4.9µg/ml	14.8µg/ml
Tezacaftor	8.5µg/ml	25.7µg/ml

Robustness

The robustness was performed for the flow rate variations from 0.9 ml/min to 1.1ml/min and mobile phase ratio variation from more organic phase to less organic phase ratio for ivacaftor and tezacaftor. The method is robust only in less flow condition and the method is robust even by change in the mobile phase ±5%. The standard samples of ivacaftor and tezacaftor were injected by changing the conditions of chromatography. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Table 18: Results of robustness for ivacaftor

Parameter used for sample analysis	Peak area	Retention time	Theoretical plates	Tailing factor
Flow rate of 1.0 mL/min	3425413	2.088	5568.2	1.0
Flow rate of 0.9 mL/min	3425282	3.111	5922.2	1.2
Flow rate of 1.1 mL/min	3517879	1.880	5868.8	1.2
Less aqueous phase	3175485	3.101	5836.2	1.2
More aqueous phase	3365431	1.881	5282.6	1.1

Table 19: Results of robustness for tezacaftor

Parameter used for sample analysis	Peak area	Retention time	Theoretical plates	Tailing factor
Flow rate of 1.0 mL/min	2029854	6.068	5359.2	1.1
Flow rate of 0.9 mL/min	1738319	7.101	5999.1	1.2
Flow rate of 1.1 mL/min	1638304	5.007	5989.2	1.1
Less aqueous phase	1973724	7.108	5387.2	1.1
More aqueous phase	2102838	5.008	5938.1	1.1

CONCLUSION

In the present investigation, a simple, sensitive, precise and accurate RP-HPLC method was developed for the quantitative estimation of tezacaftor and ivacaftor in bulk drug and pharmaceutical dosage forms. This method was simple, since diluted samples are directly used without any preliminary chemical derivatisation or purification steps. Tezacaftor and ivacaftor was freely soluble in ethanol, methanol and sparingly soluble in water. ACN, methanol and phosphate buffer pH-4.6 (10:25:65 v/v) was chosen as the mobile phase. The solvent system used in this method was economical. The %RSD values were within 2 and the method was found to be precise. The results expressed in tables for RP-HPLC method was promising. The RP-HPLC method is more sensitive, accurate and precise compared to the spectrophotometric methods. Hence, this present developed method can be used for the routine determination of tezacaftor and ivacaftor in bulk drug and in pharmaceutical dosage forms.

Conflicts of interest

None.

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