REVIEW ARTICLE

A Novel Stability Indicating RP-UPLC Method for the Estimation of Ertugliflozin in its Bulk and Tablet Dosage Forms as per ICH Guidelines

Sanapala Srinivasa Rao*, A. Vijayalakshmi

School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600117,Tamil Nadu, India

Received: 17th September, 2020; Revised: 22th October, 2020; Accepted: 21th November, 2020; Available Online: 25th Decemeber, 2020

ABSTRACT

A simple, exact, precise strategy was developed for the assessment of Ertugliflozin by reverse phase ultra performance liquid chromatography (RP-UPLC) process. Chromatographic conditions used are fixed stage like Dikma Endeversil C18 (2.1 x 50mm, 3µm). Versatile phase synthesis of 0.1% Octane Sulphonic corrosive: 30:70 v/v acetonitrile and flow rate were maintained at 0.2 ml/min, 226 nm detection frequency, 30°C temperature. The linearity analysis was conducted at 50 to 150 percent range, and R2 was found to be 0.999. The accuracy was found to be 0.6 for repeatability and 1.0 for intermediate precision. Individually, the LOD and LOQ are 2.98µg/ml and 9.97µg/ml. Ertugliflozin validation investigations have been conducted under all circumstances. The edge of virtue was more than the point of purity and exists to a reasonable level.

Keywords: RP-UPLC, Ertugliflozin, ICH, peak.

International Journal of Pharmaceutical Quality Assurance (2020); DOI: 10.25258/ijpqa.11.4.13

How to cite this article: Rao SS, Vijayalakshmi A. A Novel Stability Indicating Rp-Uplc Method For The Estimation Of Ertugliflozin In Its Bulk And Tablet Dosage Forms As Per Ich Guidelines. International Journal of Pharmaceutical Quality Assurance. 2020;11(4):530-533.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Ertugliflozin (trade name steglatro) is a type 2 diabetes (T2D) care drug and it is an inhibitor of sodium-glucose co-transporter 2 (SGLT2) therefore it belongs to the class of drugs known as gliflozin.[1] In patients with severe kidney impairment, end-stage renal disease and dialysis ertugliflozin is contraindicated. Ketoacidosis is a rare but harmful symptom of gliflozin which occurs in 0.1% patients with related studies of Ertugliflozin5,6. Ketoacidosis symptoms include nausea, wheezing, abdominal discomfort, relaxing sleep deprivation and fruity odour. Among many diabetes medications, the combination of ertugliflozin with insulin or insulin secretagogues (sulfonylureas) may result in an increased risk of low glucose levels.[2] Diuretic combination can also result in a greater risk of dehydration and low pulse.

OPTIMIZED CHROMATOGRAPHIC CONDITIONS

Instrument used	:	Waters UPLC with auto sampler and PDA as detector.
Temperature	:	Ambient
Column	:	Dikma Endeversil C18 ODS (2.1 x 50mm, 3µm)
Buffer	:	0.1% Octasulphonic acid
pH	:	3.0
Mobile phase	:	30% bufferand 70% acetonitrile
Flow rate	:	0.2 mL per min
Wavelength	:	226 nm [Figure 1(a)]
Injection volume	:	2 µL [Figure 1(b)]
Run time	:	2 min.
Retention Time	:	0.421

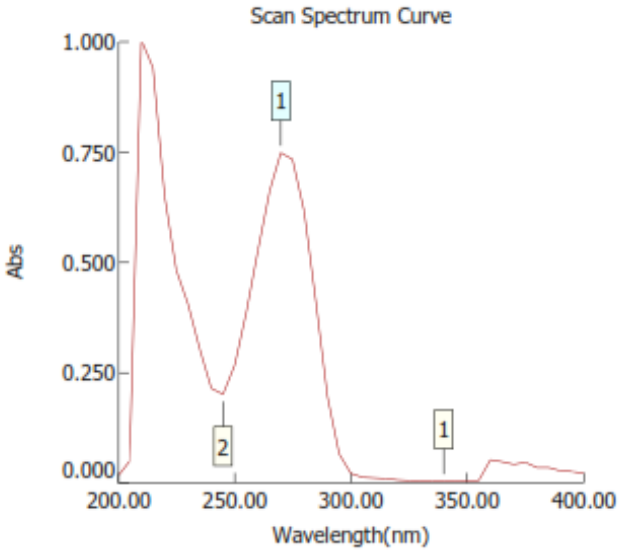


Figure 1(a): Wave length spectrum of Ertugliflozin

*Author for Correspondence: sanjayswamy317@gmail.com

Ertugliflozin Preparation in Standard and Sample Solution

Standard Solution Preparation

Add about 30 mL of diluent and sonicate to precisely calculate and transfer 10 mg of Ertugliflozin working standard into a 50 ml clean dry volumetric jar to dissolve it completely and make volume adequate with a similar solvent (Stock). 1.5 ml of the above stock arrangements are further pipetted into a 10ml volumetric flask and appropriately diluted with diluent. (Ertugliflozin 30 ppm).

Test Solution Preparation:

In a 50ml clean dry volumetric container, precisely measure 10 tablets pulverise in mortar and pestle besides transfer equivalent to 10mg Ertugliflozin (marketed formulation = 240.4mg tablet powder) test add about 30ml of diluent furthermore sonicate it up to 30 minutes to fully decompose and make volume adequate with a similar solvent. It is filtered through the 0.44 micron infusion channel at that stage (stock arrangement). In addition, 1.5mL of Ertugliflozin from the above stock arrangement is pipetted into a 10mL volumetric flask and sufficiently make with diluent. (Ertugliflozin 30 ppm).

System

Using the formulae, inject 10 µL of the standard, test into the chromatographic system, thereby calculate the areas for Ertugliflozin peaks and assess the percentage assay.

System Suitability

The following factor for the peaks due to Ertugliflozin standard arrangement should not be more than 2.0 however hypothetical plates for the peaks of Ertugliflozin in the standard arrangement should not be less than 2000.

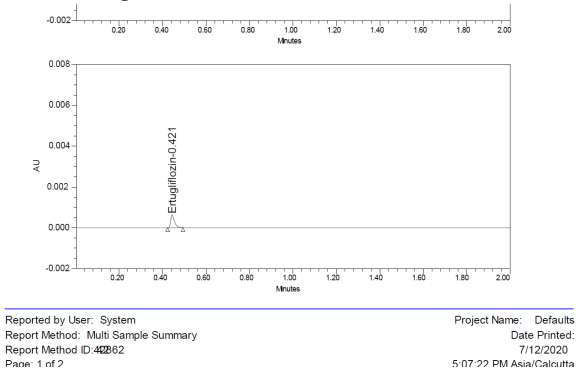


Figure 1(b): Optimized chromatogram

METHOD VALIDATION[3,4]

Precision

Method: The standard arrangements have been infused several times and the zones for each of the six UPLC infusions have been calculated. As far as possible, the percentage RSD for the region of six replicate infusions was established to be within. Results are summarized for Ertugliflozin in Table 1.

Intermediate Precision

Precision was conducted on a number of days to determine the moderate accuracy (otherwise called Ruggedness) of the technique.

The standard precision solutions were infused several times and the area was measured for each of the six UPLC injections. The percent RSD for the area of six repeat infusions was initiate to be within well beyond practicable. The results are summarized for Ertugliflozin in Table 2.

Accuracy

Preparation of sample solution:

- *For Accuracy of 50% (concerning objective Assay fixation):*

Precisely gauge 10 tablets crush in mortor and pestle and transfer identical to 5mg Ertugliflozin+ 235.4mg of pseudo treatment combination (labelled formulation = 120.2mg of tablet powder) into a 50ml clean dry volumetric flask add about 30ml of Diluent and sonicate it for up to 30 minutes to fully dissolve and render volume adequate with equal solubility. It is filtered through 0.44 micron injection channel at that point. (Stock solution). Further pipette 1.5 mL of Ertugliflozin from the above stock solution into a 10 mL volumetric flask and sufficiently dilute with a diluent. (15 ppm Ertugliflozin).

- *For Accuracy of 100% (concerning objective Assay fixation):*

Precisely measure 10 tablets, crush in mortor and pestle thereafter transfer approximately 30 ml of diluent into a 50 mL clean dry volumetric cup comparable to 10 mg Ertugliflozin + 230.4 mg of pseudo treatment combination (labelled formulation= 240.4 mg tablet powder) and sonicate it up to 30 minutes and make volume adequate with a similar dissolvable.

Table 1: Results of Precision

Injection	*Area for Ertugliflozin*
Infusion 1	347358
Infusion 2	345898
Infusion 3	349624
Infusion 4	351347
Infusion 5	345567
Infusion 6	349045
Average	341839.8
Standard Deviation	2261.2
%RSD	0.6

Table 2: Results of Intermediate Precision

Injection	*Area for Ertugliflozin*
Infusion 1	349537
Infusion 2	342874
Infusion 3	348593
Infusion 4	345487
Infusion 5	340784
Infusion 6	345292
Average	345427.8
Standard Deviation	3317.0
%RSD	1.0

It is filtered at that stage through the 0.44 micron injection tube. (Stock). In addition, 1.5 ml of Ertugliflozin from the above stock arrangement is pipetted into a 10ml volumetric flask and sufficiently dilute with diluent. (Ertugliflozin 30ppm).

- *For Accuracy of 150% (as for target Assay fixation):*

Precisely measure 10 tablets, crush in mortor and pestle and pass to a 50 mL clean dry volumetric jar equivalent to 15 mg of Ertugliflozin + 345.6 mg of pseudo treatment combination (labelled formulation= 360.6 mg tablet powder) and add about 30 mL of diluent, then sonicate it up to 30 minutes and make volume adequate with a similar dissolvable. It is filtered at that point through the 0.44-micron injection (stock) tube. Additional 1.5 ml of Ertugliflozin pipette from the above stock solution into a 10ml volumetric jar and sufficient diluent dilutions are carried out. (Ertugliflozin 45 ppm).

Acceptance Criteria

For each stage, the percent recovery should be between 98.0 and 102.0%.

Linearity: The linearity was calculated by the calibration solutions, diluent preparation. The regression curve was calculated using the least square method by plotting peak area versus concentration. Slope, correlation coefficient, F meaning, relative standard slope deviation percentage, and Y-intercept calibration curve were determined. The sample had to be injected 5 times. The findings were seen in linearity, (Figure 2).

LoD and LoQ: LoD value was 0.429 and LoQ value was 0.421 respectively. The results were mentioned in Figure 3(a) and 3(b).

Robustness

In order to determine the effect on the system, temperature variation was made as part of the Robustness, intentional change in the flow rate, mobile phase composition. The rate of flow ranged between 0.18 mL/min and 0.22 mL/min.

DEGRADATION STUDIES[4,7]

The Guidelines for Stability Testing of New Drugs and Products of the ICH require performance tests to be completed

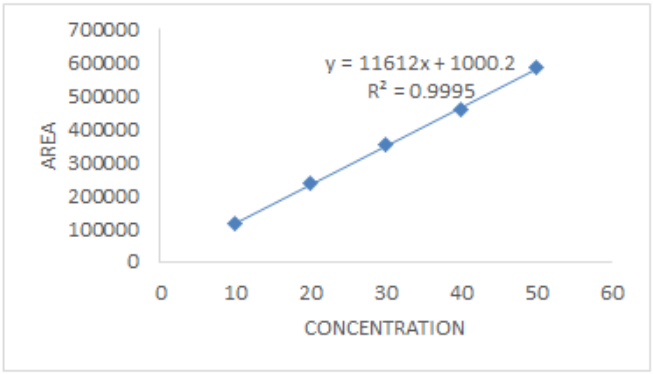
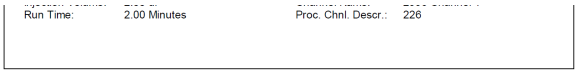


Figure 2: Calibration curve



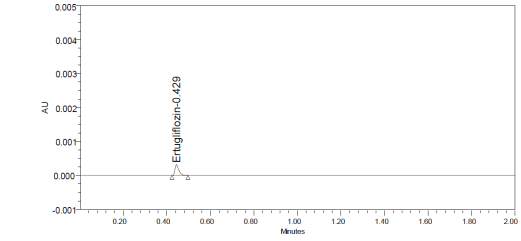


Figure 3(a). LOD chromatogram

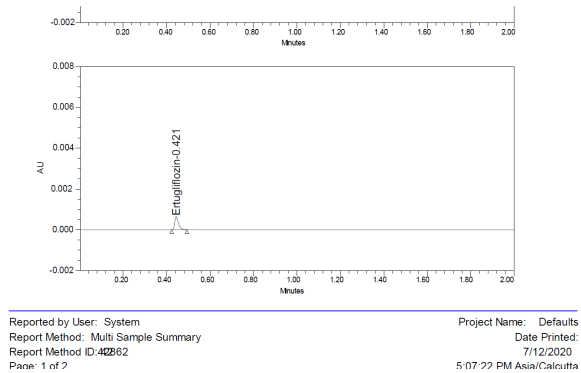


Figure 3(b): LOQchromatogram

Table 3: The results of accuracy

Concentration	*Area*	*Amount Added (mg)*	*Amount Found (mg)*	*% Recovery*	*Mean Recovery*
50%	175573	5	5.05	101.07	
100%	347420	10	10.00	99.99	100.22
150%	518990	15	14.94	99.58	

Table 4: Results of Degradation studies

	Ertugliflozin				
Degradation Studies	*Area*	*Percent Degraded*	*Purity Angle*	*Purity Threshold*	*Peak purity*
Standard	346387				
Acid	316528	8.62	0.339	1.250	Passes
Base	338212	2.36	0.208	1.252	Passes
Peroxide	324461	6.33	0.123	0.262	Passes
Thermal	340602	1.67	0.180	0.255	Passes
Photo	334402	3.46	0.168	0.253	Passes

in order to elucidate the inherent stability characteristics of the active substance. The purpose of this study was to work out Ertugliflozin stress degradation studies using the suggested methods, such as acidic, peroxide degradation, alkaline hydrolytic degradation, thermal degradation and oxidative degradation and the results were illustrated in Table 4.

CONCLUSION

A new method for the estimation of Ertugliflozin by the UPLC method has been developed. Using column Dikma Endeversil C18 ODS (2.1 x 50mm, 3µm), the flow rate was 0.2 ml/min, the mobile phase ratio was 30:70% buffer and Acetonitrile, the detection wavelength was 226nm, the chromatographic conditions for the separation of Ertugliflozin were successfully established. It was found that retention times were 0.421. Ertugliflozin percent purity was found to be 99.82%, respectively. By studying different media and circumstances, the UPLC method has been optimised. In all the formulations, the sample recoveries were in excellent accordance with their respective labelled claims, and in all appropriate parameters, the proposed method was validated according to ICH guidelines. The proposed method for the assay in the commercially available tablet formulation of the popular anti-diabetic drug Ertugliflozin is simple, accurate, economical, and convenient. It can easily be used in the API, in-process samples, and the finished tablet formulation for routine quality control for monitoring the assay.

ACKNOWLEDGEMENT

I immensely thankful to the Institution, School of Pharmaceutical Sciences, VISTAS, Chennai for providing the gift sample of Ertugliflozin and chemicals to carry out the research work.

REFERENCES

1. Katzung BG, Masters SB, Trevor AJ. Basic and clinical pharmacology. 13th Edn. McGraw Hill Medical, New York, 2015; pp 736–742.
2. Ghadir A Khalil, Ismail Salama, Mohammed S Gomaa and Mohammed A Helal, Validated Rp-Hplc Method For Simultaneous Determination Of Canagliflozin, Dapagliflozin, Empagliflozin and Metformin,IJPCBS 2018; 8(1), 1-13.
3. Breaux J and Jones K: Understanding and implementing efficient analytical method development and validation. Journal of Pharmaceutical Technology. 2003; 5, 110-114.
4. ICH Guideline: Y. Hiyama, D.Keire, analytical procedure development and revision of Q2(R1) analytical validation, june 2018.
5. Harshalatha P, Chandrasekar MV. A novel RP-HPLC method for simultaneous determination of Ertugliflozin and Sitagliptin in bulk and tablet dosage form. International journal of research in pharmaceutical sciences. 2019; Vol. 9(3), 1042-1050.
6. Kumari, K.S., Bandhakavi, S. Development and validation of stability-indicating RP-HPLC method for the simultaneous determination of ertugliflozin pidolate and metformin hydrochloride in bulk and tablets. Futur J Pharm Sciences. 2020; 6, 66.
7. Mohan Goud V, Swapna G. Stability indicating method development and validation for the estimation of ertugliflozin and metformin in bulk and pharmaceutical dosage form by ultra-performanceliquid chromatography. 2019; 11(1), 173-178.