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EMPAGLIFLOZIN: RP-HPLC BASED ANALYTICAL METHOD DEVELOPMENT AND VALIDATION

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ABSTRACTS

The investigation focuses on developing an efficient analytical method for the quantification of empagliflozin in pharmaceutical dosage forms, as there is currently no pharmacopoeial method available for the drug. The newly developed method was validated following ICH guidelines. A C18 column was used for analysis, with a mobile phase consisting of 0.1% trifluoroacetic acid solution and acetonitrile in a 70:30 (v/v) ratio at pH 4.8. The method demonstrated a highly linear calibration curve ($r^2 > 0.999$) over a concentration range of 0.025 to 30µg/mL The limits of detection (LOD) and quantification (LOQ) were found to be 0.020 µg/mL and 0.061 µg/mL, respectively. Recovery studies showed excellent accuracy, with recovery values ranging from 98.0% to 100.13%. The precision and accuracy of the method were within 2%, confirming its suitability for routine pharmaceutical analysis. The stability of the drug solution was tested at both refrigerated and ambient room temperatures, with mean accuracy above 98%. The method was applied to quantify empagliflozin in raw API and tablet formulations, yielding mean assay values for raw empagliflozin ranging from 99.29% ± 1.12 to 100.95% ± 1.69, and for tablet brands ranging from 97.18% ± 1.59 to 98.92% ± 1.00. These findings demonstrate that the developed method is reliable and accurate for the quantification of empagliflozin in both raw and pharmaceutical dosage forms.

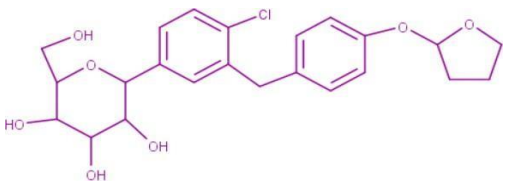
KEYWORDS: Bulk dosage form, empagliflozin, HPLC, method development, validation.

INTRODUCTION

Method development and validation are essential steps in pharmaceutical analysis to ensure that the results produced by the developed methods are reliable, accurate, suitable, and robust for routine use. In pharmaceutical quality control, various analytical parameters are regularly assessed to evaluate the quality of dosage forms. In this context, regulatory bodies play a pivotal role by requiring drug manufacturing companies to provide comprehensive validation protocols for analytical methods.

Type II diabetes mellitus has become a major global health issue, ranking as the seventh leading cause of death worldwide. To manage hyperglycemia associated with this condition, antidiabetic medications are commonly prescribed. Among these, traditional hypoglycemic agents such as metformin, meglitinides, thiazolidinediones, and sulfonylureas have well-established therapeutic profiles in the treatment of type 2 diabetes. Empagliflozin, chemically known as (1-chloro-4-[β-D-glucopyranos-1-yl]-2-[4-([S]-tetrahydrofuran-3-yl-oxy) benzyl]-benzene), is a sodium-glucose cotransporter 2 (SGLT2) inhibitor that exerts glucosuric effects, making it an important agent in the management of diabetes. Physically, empagliflozin appears as a yellowish to whitish crystalline solid and is non-hygroscopic.

To date, there has been no reported analytical method development and validation for empagliflozin using trifluoroacetic acid as the mobile phase in normal-phase high-performance liquid chromatography (HPLC). This manuscript outlines the key stages in the analytical method development lifecycle, from the initial development phase to the final validation stage, as per the guidelines set by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The study aims to develop a straightforward, rapid, reliable, sensitive, accurate, and robust method for quantifying empagliflozin in both raw and pharmaceutical dosage forms, including the validation of the proposed method.[1-62]



Structure of Empagliflozin

MATERIAL AND METHODS

The investigators sourced the amount of empagliflozin from Hyderabad-based Aurobindo Laboratories and Hyderabad-based Spectrum Pharma Research Solutions.

HPLC assay

Chromatographic conditions

When reverse phase liquid chromatography separation was first made an effort, the drug did not react as expected. Different ratios of acetonitrile and water, thenphosphate buffer and acetonitrile as mobile phases were used. To improve drug elution, the organic conformation of the mobile phase was also examined. [The pH level of the mobile phase is a vital factor in improving its tailing factor. A mixture containing water and acetonitrile was then created at a flow rate of around 1.0mL/min. An ODS column was then used to reduce the peak's tailing. For the PDA detector, 224 nm was used as the detecting wavelength. About 4.8 minutes proved to be the retention time. Mobile Phase selected as Acetonitrile:water70:30 v/v, pH was maintained at 4.8(+/-0.5) at a Wave Length-224nm for a Injection Volume 20ml adjusted the Flow rate 1ml/min with a Run time 7mins showed Retention time-4.8mins

Preparation of stock solutions

The stock solution of empaglifluzin was prepared by dissolving a precise amount of potassium dihydrogen phosphate in 0.05M. This mixture was then made up with methanol to form a final concentration of 0.2 mg. mL-1. The stock was then diluted with mobile phase to obtain a final volume of 0.01-30 g-1 for linearity and calibration curve.

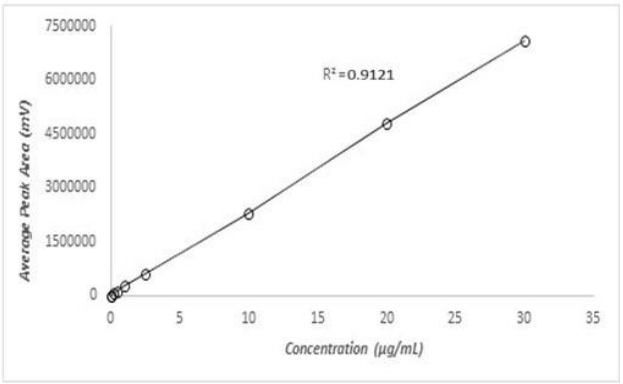
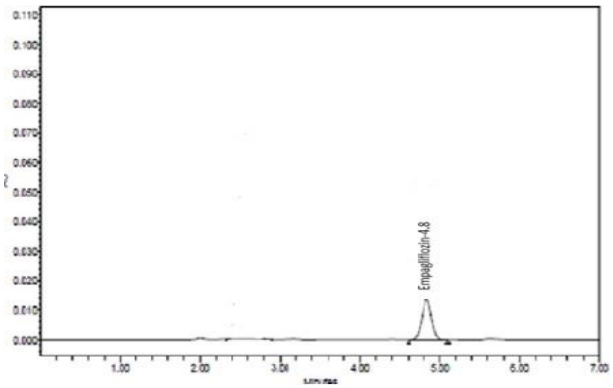


Fig: Linearity of empagliflozin.

Preparation of working solution

Average of twenty tablets were weighed and finely crushed. The equivalent content of each tablet (10 mg) was transferred into 50 mL volumetric flask and make up to the volume with mobile phase. From the prepared solution, 5 mL was added in 100 mL volumetric flask to obtain the final concentration of 0.01 mg mL-1.



Method validation

System suitability

The validation of the HPLC method was conducted as per ICH (2005) and Food and Drug Administration (FDA) (2001) guidelines. System suitability and specificity of standard solutions of empagliflozin at 20 µg mL-1 was determined. The acceptance criterion according to United States Pharmacopoeia (USP) (2014) of percent relative standard deviation (% RSD) for peak area and tailing factor was 2000 and retention time was greater than 2.0.

Linearity: Nine standard solutions from 0.025 to 30 µg mL-1 strength (0.025, 0.05, 0.25, 0.5, 1, 2.5, 10, 20 and 30 µg mL-1) were analyzed for linearity. The calibration curve was constructed by plotting the peak area against concentration in µg mL-1.

Table 1: System suitability parameters (n = 6).

Parameter	Findings	Limits
Peak Area (mean)	4701227	-
% RSD	0.005	<2.0
Retention time (min)	5.452	<2.0
% RSD	0.364	<2.0
Theoretical Plates	2314	>2000
USPtailing factor	1.12	<2.0
Resolution	NA	

Specificity

It is analyzed by observing any interfering peak near the API by eluting the drug solution along with the blank (mobile phase) and the placebo mixture. Placebo mixture was prepared by adding the common tablet formulation ingredients including talc, magnesium stearate, microcrystalline cellulose, starch and lactose in concentration of 1 mg mL-1.

Precision and Accuracy

Precision and Accuracy The accuracy and precision of the method was established by performing recovery run tests using three different concentration levels with six replicate analysis (n = 6). Results of accuracy and precision were calculated and expressed as % accuracy and % coefficient variation of analytes respectively. Method is said to be precise and accurate when the percent coefficient of variation (CV) and % mean accuracy are found to be <2% and 90-110 % respectively.

Reproducibility	Added Conc (µgmL^{-1})	Conc found (µgmL^{-1}) (Mean ± SD)	Percent Mean Accuracy (%)	% CV forprecision (<2%)
	0.05	0.047±	98.00	2.04
Precision		0.001		
Interday	15	14.84 ±	99.33	0.73
		0.110		
	30	29.88 ±	99.93	1.27
		0.370		
	0.05	0.052±	100.04	1.96
Precision		0.001		
Intraday	15	14.02 ±	100.13	0.28
		0.033		
	30	30.01 ±	100.03	1.29
		0.390		

Limit of detection (LOD) and limit of quantification (LOQ) LOD and LOQ values were calculated from calibration plot using the SD (σ) and slope (S). The expressions are given below; LOD = 3.3 σ/S (Equation 1) LOQ = 10 σ/S (Equation 2)

Robustness

It was determined by making change in temperature of column (30ºC ± 3ºC), rate of flow (± 0.2 mL min−1) and λ (± 2 nm).

Changes in chromatographicconditions Using 5.0µgmL-1		Concentrationobtained (µgmL-1) (Mean±SD)	CV (%)	Mean Accuracy (%)
Flowrate (mL min-1)	0.6	4.92± 0.06	1.24	98.4
	0.8	4.98± 0.08	1.26	99.6
	1.0	4.98± 0.14	2.78	99.6
Colum nTemperature (ºC)	33	5.05±0.12	2.38	101.0
	30	4.98±0.07	1.31	99.6
	27	4.99±0.06	1.15	99.8
Detection wavelength(nm)	226	4.97± 0.09	1.82	99.4
	224	5.01± 0.12	2.45	100.2
	222	4.95± 0.06	1.34	99.0

RESULTS

Method was validated for each and every parameter as recommended by ICH guidelines of method development and validation. The data of various validation parameters are summarised in table 1-3. The linearity of the underlying analytical procedure is provided in fig. 2

keeping the drug concentration and mean peak area as X and Y variables. The coefficient of regression for linearity was found to be 0.999 with intercept and standard error values of 19085.15 and 28350.16 respectively. The ANOVA (95% CI) was applied to the calibration data, indicating the gradual decrease of peak area with respect to the drug concentration from 0.025 to 30 µg mL-1 (p=0.519). Figs. 3, 4 and 5 illustrate the chromatogram of blank, placebo and drug samples, reflecting the drug specificity during analysis. Results show that the proposed method is accurate, précised and robust as no variation was observed upon minor changes in the proposed protocol of the procedure. Moreover, drug was found to be stable in solvent at ambient and refrigerated conditions, details are given in table 4. Pharmaceutical assay of empagliflozin in three samples of raw material and commercial tablet brands is given in table 5.

DISCUSSION

Method validation

Due to recent advancement in analytical technologies, the primary need is to develop an effective, reliable and selective quantification method for active pharmaceutical ingredients. This reliability and accuracy in analytical techniques is extremely desirable as it affects the quality characterization of many pharmaceuticals. Various analytical methods have been used for drug estimation however, HPLC is still popular and being utilized successfully for the quantification of many chemicals by researchers. Therefore, in the present study, a simple, accurate and sensitive HPLC method has been developed and validated as per ICH recommendations for empagliflozin in the bulk powder. At present, no pharmacopoeial method is available for the determination of empagliflozin while numerous brands of empagliflozin are available in the commercial market, manufactured by national/local pharmaceutical companies. The same developed method was also applied to the pharmaceutical assay of commercially available empagliflozin tablets (10 mg). After several trials during method development, the composition (70:30 v/v) ratio of trifluoroacetic acid with acetonitrile was found to be suitable for mobile phase. Empagliflozin has estimated previously using orthophosphoric acid in combination with, acetonitrile with water and methanol with phosphoric buffer of pH 3. The chromatographic separation was achieved using C18 column giving sharp, symmetric peak with retention time of 5.470 ± 0.378 minutes. The UV detection of eluent was recorded at λ 224 nm. Further to monitor the system suitability performance the number of theoretical plates and tailing factor were observed and temperature was maintained around 30ºC. The obtained results for system suitability were in close agreement with the previous studies conducted for various medicinal agents. Calibration data of the empagliflozin showed good linearity within concentration range of 0.025 µg mL-1 to 30 µg mL-1. Moreover upon statistical analysis, insignificant variation was maintained around 30ºC. The obtained results for system suitability were in close agreement with the previous studies conducted for various medicinal agents. Calibration data of the empagliflozin showed good linearity within concentration range of 0.025 µg mL-1 to 30 µg mL-1. Moreover upon statistical analysis, insignificant variation was observed among the peak area, slope, and intercept to the corresponding drug concentrations. Alquadeib in 2019 had proposed a new analytical method for the estimation of the diclofenac sodium in a pharmaceutical dosage form. Author was further declared the reproducibility of the procedure by comparing and fitting the ANOVA to the regression plots. Probability value showed the insignificant differences in the slopes and intercepts among the calibration curves. The regression equation of the plot y = 236893x + 6136.1 with observed among the peak area, slope, and intercept to the corresponding drug concentrations. Alquadeib in 2019 had proposed a new analytical method for the estimation of the diclofenac sodium in a pharmaceutical dosage form. Author was further declared the reproducibility of the procedure by comparing and fitting the ANOVA to the regression plots. Probability value showed the insignificant differences in the slopes and intercepts among the calibration curves. The regression equation of the plot y =236893x + 6136.1 with goodness of fit value of 0.9998 was achieved, demonstrating strong correlation. The values of limits of detection and quantification (LOD and LOQ) were calculated through analytical curves. The minimum detection and quantification limits were found to be 0.020µgmL-1 and 0.061µg mL-1, respectively. Previously Shyamala and co-workers reported HPLC technique to estimate the empagliflozin in raw and dosage form using 0.1% orthophosphoric acid and acetonitrile. The computed values of LOD and LOQ were 0.068 µg mL-1 and 0.207µg mL-1 correspondingly (Shyamala et al., 2016). In our study, the lower values of detection were observed due to the appropriate selection and composition of mobile phase.

CONCLUSION

The proposed developed analytical method has been found to be accurate, reliable and cost-effective for the determination of empagliflozin in raw and the pharmaceutical dosage form. It is robust and specific therefore could be successfully utilized by regulatory bodies, pharmaceutical industries and research laboratories as no any official or pharmacopoeial method is available. This newly developed method further opens future prospects for bioanalytical method development.

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