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REVIEW ON SIMULTANEOUS ESTIMATION OF ANTIDIABETIC DRUG BY HPLC METHOD

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ABSTRACT

High performance liquid chromatography (HPLC) is an important qualitative and quantitative technique, generally used for the estimation of pharmaceutical and biological samples. It is the most versatile, safe, reliable and rapid chromatography technique for quality control of drug components. This article was prepared with the objective of reviewing the use of HPLC for the chromatographic analysis of antidiabetic drugs belonging to the category of sodium-glucose cotransporter (SGLT2) inhibitors (Canaglifozine, Dapagliflozine, Empagliflozine, Ertugliflozine).

KEYWORDS: HPLC, Analysis, Antidiabetic drugs, Canaglifozine, Dapagliflozine, Empagliflozine, Ertugliflozine, SGLT2 inhibitors.

INTRODUCTION

Diabetes mellitus (DM) is a complex chronic disease associated with high blood glucose status, or hyperglycemia, as a result of deficiencies in insulin secretion, action, or both.[1] The clinical diagnosis of diabetes depends on one of the four plasma levels Glucose Criteria (PG): (i) elevated fasting plasma glucose (FPG) (> 126 mg / dL), (ii) 2 hr PG during a 75 g oral glucose tolerance test (OGTT) (> 200 mg) / dL), (iii) random PG (> 200 mg / dL) with classic signs and symptoms of hyperglycemia, or (iv) hemoglobin A1C level> 6.5%.[2,3]

The main classes of oral antidiabetic drugs include biguanides, sulfonylureas, meglitinide, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter inhibitors (SGLT2), and α-glucosidase inhibitors.[4,5,6]

The present study was carried out with the objective of studying the different HPLC methods developed for the determination of antidiabetic drugs of the SGLT2 class in bulk and in various pharmaceutical forms. The present study also included the method developed for the estimation of drugs individually or in a combined formulation with other oral hypoglycemic agents.

High Performance Liquid Chromatography (HPLC)

High performance liquid chromatography (HPLC) is derived from classical column chromatography and is today one of the most important tools in analytical chemistry. The principle is that a sample solution is injected into a column of a porous material (stationary phase) and a liquid (mobile phase) is pumped under high pressure through the column. Sample separation is based on differences in migration rates through the column that result from the different distribution of the sample between the stationary and mobile phase.[7,8] High-performance liquid chromatography is more versatile than chromatography of gases because (a) it is not limited to volatile and thermally stable samples, and (b) the choice of mobile and stationary phases is broader.[9,10,11]

High performance liquid chromatography (HPLC) is an essential analytical tool in the evaluation of pharmaceutical products.[12,13] Validation is the process of establishing the performance characteristics and limitations of a method and identifying influences that can change these characteristics. and in what size. This article examines the use of HPLC for the chromatographic analysis of antidiabetic drugs (sodium glucose cotransporter inhibitor (SGLT2)) Canaglifozine, Dapagliflozine, Empagliflozine, Ertugliflozine.

Method Validation

Methods should be validated to include consideration of characteristics included in the International Conference on Harmonization (ICH) guidlines addressing the validation of analytical methods. Analytical methods outside the scope of the ICH guidance should always be validated.[14]

HPLC Analysis of Dapagliflozin

Dapagliflozin is a sodium-glucose cotransporter 2 inhibitor indicated for the treatment of type 2 diabetes mellitus. When combined with diet and exercise in adults, dapagliflozin helps improve glycemic control by

inhibiting the reabsorption of glucose in the proximal tubule. of the nephron. and causing glucosuria.

In an experiment by Debata et al., (2017) a new technique of high-performance reverse-phase liquid chromatography of Dapagliflozin was established, simple, selective, precise, fast and precise according to the ICH guidelines. RP-HPLC was performed on a Waters C18, particle size 5 µm, 25 cm x 4.6 mm, with phosphate buffer and acetonitrile in the ratio of 60:40 v / v as mobile phase and a flow rate of 1.0 ml min-1. UV detection was done at 237 nm. Total run time was 6.0 min. Dapagliflozin retention time was found to be 3.461 minutes. The validation of the developed method was carried out in accordance with the USP and ICH guidelines. Method validation revealed that the method was fast, accurate, precise, reliable, and reproducible. Linear calibration graphs were obtained in the concentration range 10-60 µg / mL for Dapagliflozin. The limit of detection was 0.02 µg / mL and the limit of quantification was 0.06 µg / mL for Dapagliflozin. The high recovery and low coefficients of variation confirmed the efficiency of the process in the pharmaceutical form. The results suggested that the method developed was a suitable method for analysis, purity that could aid in the analysis of Dapagliflozin in different formulations.[15]

In another study conducted by Basha and Sravanthi (2017), the estimation of dapagliflozin was performed using the reverse phase high-performance liquid chromatography (RP-HPLC) technique in bulk and tablet formulation to develop and validate a simple method, selective, precise and exact method. The proposed method used hypersile BDS chromatographic conditions (250 mm × 4.6 mm, 5 µ), the mobile phase was buffer: acetonitrile ratio (60:40), the flow rate was maintained 1 ml / minute, the column temperature was it was set at 30 ° C, the detection wavelength was 245 nm and the diluent was the mobile phase. Their results were found far below the acceptance criteria when they injected the standard solution system 5 times and studied the suitability parameters. The linearity study was carried out taking levels of 25-150% and the R2 value was equal to 0.999, the precision was equal to 0.5 for repeatability and 0.31 for intermediate precision. The recovery rate was found to be 99.89%. The limit of detection and the limit of quantification were 0.60 µg / ml and 1.81 µg / ml, respectively. The% purity was found to be 99.71%. A dapagliflozin degradation study was performed and it was concluded that the purity threshold was above the purity angle and within the acceptable range.

The results of the forced degradation studies showed that the main degradation route is acid hydrolysis followed by alkali, oxidation, thermal, photolytic and neutral, respectively. The developed method concluded that dapagliflozin was stable under neutral, photolytic, thermal and oxidative stress conditions and unstable under acidic and alkaline conditions.[16]

Verma et al., (2017) in their study developed a precise, exact and reproducible stability analysis method by RP-HPLC to estimate dapagliflozin in API and pharmaceutical form. In the experiment, a suitable separation was performed using Agilent C18 (4.6 ml (mm) * 150.5 µm (micron), acetonitrile: dipotassium hydrogen phosphate with adjusted pH of OPA-6.5 (40: 60% v / v) as mobile phase with a flow rate of 1 ml / min (milliliter / minute) and the effluent was monitored at 222 nm (nanometers) using a photodiode array detector. dapagliflozin API and dapagliflozin were 3,160 min (minute) and 3,067 min (minute). According to their results, the linearity for dapagliflozin was found in the range of 50-150 µg / ml (microgram / milliliter) (R2 = 0.99) respectively. The precision of this method was evaluated at 50%, 100% and 150%. The recovery rate of dapagliflozin API and the tablet was found to be between 99.00 and 99.99% and 98%., 50-99.99% respectively Precision studies and deviation values were performed Relative standard were less than 2. The method was found to be robust Overall, the proposed method was found to be specific, exact, accurate and robust and could be used for the estimation of dapagliflozin in API and dosage form.[17]

According to a study by Mante et al., (2018) the RP-HPLC method was developed for the determination of Dapagliflozin in tablet dosage form. The method was validated and turned out to be simple, sensitive, accurate and precise. The chromatographic separation was achieved by isocratic mode with a mixture of acetonitrile: 0.1% triethylamine (pH-5.0) in the ratio of 50:50 v / v as mobile phase using the Princeton C18 column at a flow rate of 1 ml. / min and detection wavelength of 224 nm. Using optimized chromatographic conditions, the drug retention time was found to be 5.163 min. The proposed method obeyed the Beer-Lambert law in the concentration range of 10-70µg / mL, with a correlation coefficient value of 0.999. The estimated average percentage amount of drug was 100.57%, considered good according to the label statement of the marketed tablet formulation. Validation parameters such as accuracy, precision, robustness, robustness, linearity, and range were studied for the proposed method and found to be within limits. Stress tests were also performed under various conditions such as pH (acid / base), oxidation, temperature, light, humidity, etc.[18]

In another work by Aswini et al., (2018) a rapid, specific, accurate and precise reversed phase liquid chromatography (RP-HPLC) method was developed and validated for the simultaneous determination of Dapagliflozin and Saxagliptin in bulk. and pharmaceutical dosage form. The successful chromatographic separation of Dapagliflozin and Saxagliptin was carried out with Inertsil-ODS, column C18 (250 × 4.6 mm; 5µm) with mobile phase consisting of a mixture of methanol buffer and potassium dihydrogen phosphate in a ratio of 45:55 v. / v delivered

at a flow rate of 1.0 ml / min. The eluents were monitored by the PDA detector and the maximum values were measured at 210 nm. The retention times for dapagliflozin and saxagliptin were 4.707 minutes and 6.684 minutes, respectively. The analytical method was validated according to the ICH guidelines (ICH, Q2 R1). The linearity study of Dapagliflozin and Saxagliptin was found in the concentration range of 20-70 µg / mL and 20-70 µg / mL, respectively, and the coefficient of variance was 0.999 for both drugs. The recovery rate was 100.37% and 100.16% for dapagliflozin and saxagliptin, respectively. The LOD was 0.109 µg / mL and 0.58 µg / mL and the LOQ was 0.332 µg / mL and 1.77 µg / mL for Dapagliflozin and Saxagliptin, respectively. It was inferred that the developed method has been successfully applied for the simultaneous estimation of dapagliflozin and saxagliptin in bulk and their commercial pharmaceutical forms and could be used for routine analysis of drugs studied in quality control laboratories.[19]

HPLC analysis of Canagliflozin

Canagliflozin is a C-glycosyl compound that is used (in its hemihydrate form) for the treatment of type II diabetes by inhibiting the sodium-glucose transport protein subtype 2. It is a C-glycosyl compound, a member of the thiophenes and an organofluoric compound.

In an investigation, Kaur et al., (2016) attempted to develop a simple, authentic and stable HPLC method to estimate canagliflozin in bulk and tablet dosage form. In the methodology, the research investigated the use of a mobile phase consisting of acetonitrile: orthophosphoric acid in a ratio of 55:45 v / v and for this a flow rate of 1 ml / min with an injection volume of 20 µL was selected. study. The method was validated against Linearity, Precision, Precision, Robustness, Force, Limit of Detection (LOD) and Limit of Quantification (LOQ). The separation was obtained at a temperature of 30 ° C and the eluents were observed by means of a photodiode array detector at 290 nm. A linear range of 1-6µg / mL with a correlation coefficient of 0.998 explains a good linear relationship between area and concentration on the calibration curve. The retention time obtained was 6.29 min. A recovery of Canagliflozin in the tablet formulation was observed in the range of 99.6-99.8%. The percentage dose of Canagliflozin (INVOKANA®) tablets was found to be 99.92%. Based on their findings, the researchers proposed that the present method is defined, meticulous and reproducible and can be used for routine testing of Canagliflozin in bulk and in pharmaceutical form.

The values for accuracy, precision, robustness, robustness, LOD and LOQ were within limits. Canagliflozin is very sensitive so it is unstable to alkaline, acidic, oxidative, thermal and photographic light. Statistical analysis of the results clearly demonstrates that the method is suitable for the determination of Canagliflozin in bulk and in tablets without any interference from degradation products, and is approved for routine use in laboratories in the quality control industry. 20 However, the mobile phase used in the study employed has a very high ration of orthophosphoric acid which can cause the column to clog due to precipitation.

In another investigation, Marella et al., (2017) planned their studies with the aim of developing a simple, specific and precise reverse phase high-resolution liquid chromatography method for the determination of Canagliflozin in pharmaceutical and bulk forms. As a result of their effort, the Canagliflozin peak was found to elute at 4.4 minutes using the mobile phase. The calibration curve was a linear combination of 0.02% formic acid: acetonitrile (40:60) at a flow rate of 1.2 ml / min and the eluents were monitored at 230 nm. Under other chromatographic conditions, the ODS-3 column (250 x 4.6 mm, 5 µ) was used. The mean percentage dose was found to be 98.2. According to the ICH guidelines, it has been proven to validate the method and can be used for the determination of Canagliflozin in bulk and in pharmaceutical form with an LC-MS compatible mobile phase composition in a short period of time.[21]

Singh et al., (2019) develop, validate and compare a spectrophotometric method and a high performance liquid chromatography method to estimate canagliflozin in the form of bulk and tablet doses. Spectrophotometry and high-performance liquid chromatography were performed using standard instrumental parameters, which were optimized. The optimized mobile phase ratio in low pressure gradient mode high performance liquid chromatography was 50: 50% v / v acetonitrile: orthophosphoric acid (0.01 M), providing a sharp peak with a short retention time of 4,732 minutes. In spectrophotometric analysis, methanol as solvent provided adequate molar absorption at λmax of 280 nm. The results indicated that both spectrophotometric methods and high performance liquid chromatography were linear, accurate, precise, robust and robust with RSD values below 2% and the recovery percentage was within standard limits (90-110%). Both methods were statistically insignificant at 95% confidence intervals ($p < 0.05$) with each other. The proposed methods have been shown to be very effective and could be used for the quantification of canagliflozin formulations and bulk tablets for routine testing.[22]

In the study carried out by Parida et al., (2018) a method was developed for the estimation of Canagliflozin in pharmaceutical forms using high-performance reverse-phase liquid chromatography. Analysis was performed using a C18 column with an internal diameter of 250mm x 4.6mm, a particle size of 5 µm) and an Agilent LC1220 HPLC machine with UV detection (VWD detector) at 293 nm. The mobile phase was used as a buffer methanol: phosphate (pH adjusted to 4 with

orthophosphoric acid) (65:35 v / v) at a flow rate of 1 ml / min. As a result of the procedure, the chromatogram is separated and indicates the retention time of 2,980 min. The recovery of Canagliflozin was found to be between 99.33 and 99.92%. The developed method was also validated according to the ICH guidelines. Linearity was performed for Canagliflozin in the range of 10-125 µg / mL with a correlation coefficient of 0.999. The drug recovery rate was achieved in the range of 98-102% which is within the acceptance criteria.[23]

HPLC Analysis of Empagliflozin

Empagliflozin is a C-glycosyl compound consisting of a beta-glucosyl residue having a (4-chloro-3- {4 - [(3S) - tetrahydrofuran-3-yloxy] benzyl} phenyl group at the anomeric center. a group C - composed of glycosyl, aromatic ether, a tetrahydrofuran ether, and a member of the monochlorobenzenes. Empagliflozin works by helping the kidneys remove glucose from the bloodstream. Empagliflozin is used in conjunction with diet and exercise to improve blood blood glucose control in adults with type 2 diabetes mellitus.

In a study by Siridevi et al., (2019) Empagliflozin was estimated in bulk and tablet dose form using the HPLC method. Chromatography was performed on the Enable C18G column (250 x 4.6 mm i.d., 5 µ). Methanol and water in a ratio of 70: 30% v / v as mobile phase at a flow rate of 1 ml / min and the effluent was controlled at 233 nm. The drug retention time was found to be 6.2 minutes. The method was effectively applied to empagliflozin tablets and the recovery rate of empagliflozin from the tablet formulation was found to be 99.65 to 99.89%. The method was also validated according to ICH guidelines and the method was found to be simple, accurate, precise and reproducible and therefore can be applied for routine quality control analysis of empagliflozin in the form pure dosage and tablets. Statistical results and low% RSD values indicate that the method is precise, accurate, robust, specific, and can be used in a wide range of concentrations. All of these key features suggest that this method can be considered advantageous over other methods.

Godasu and Sreenivas (2017) performed an HPLC analysis for the simultaneous estimation of Metformin and Empagliflozin. The chromatographic conditions were developed successfully and the Symmetry C18 column (4.6 x 150 mm) of 5 µ was used, the flow rate was 1 ml / min, the mobile phase ratio was (70:30 v / v) methanol : phosphate buffer (KH2PO4 and K2HPO4) phosphate pH 3 (The pH was adjusted with orthophosphoric acid), the detection wavelength used was the Waters HPLC autosampler. Retention times were found to be 2.403 minutes and 3.907 minutes for metformin and empagliflozin, respectively. The% purity of metformin and empagliflozin was found to be 99.87% and 100.27%, respectively. The analytical method was validated according to the ICH guidelines. The recovery percentage was found to be 99.56% and 99.48%. The LOD value was 2.17 and 0.0372 and the LOQ value was 6.60 and 0.1125 respectively. The method was found to be simple, precise, accurate and sensitive for the simultaneous estimation of metformin and empagliflozin in dosage forms.[25]

Shyamala et al., (2016) in their work described the development and validation of a reverse phase HPLC (RP-HPLC) method that indicates stability for the analysis of Empagliflozin in its API. The proposed method uses the Hypersil BDS column Mobile phase 0.1% OPA: acetonitrile in the ratio of 70:30 and the flow rate was maintained at 1 ml / min, the detection wavelength was 233 nm and the temperature of the column was set at 30 ° C. The developed method was successfully validated for various validation parameters according to the ICH guidelines. The stability of the drug was determined by studying the degradation of the drug under acidic, alkaline, peroxide, neutral, thermal and UV conditions. Therefore, a simple, selective, sensitive and accurate RP-HPLC method indicating stability has been developed and validated for the analysis of the Empagliflozin API. Furthermore, the method was found to be linear, precise, exact, and robust. Degradation studies reveal the stability of the drug. Therefore, the proposed method can be used safely and successfully for the estimation of the API of Empagliflozin in routine analysis.[26]

Analysis of Ertugliflozin by HPLC

Ertugliflozin belongs to the class of potent and selective sodium-dependent glucose cotransporter (SGLT) inhibitors, more specifically type 2, which is responsible for approximately 90% of glomerulus glucose reabsorption. Compounds that inhibit the sodium-glucose transporter 2. They lower blood sugar by preventing the reabsorption of glucose by the kidneys and are used in the treatment of type 2 diabetes mellitus.

In an investigation, Babu et al., (2018) performed a simultaneous estimation of Ertugliflozin (ETR) and Sitagliptin (SGT) in bulk and its dosage form using the RP-HPLC method. A determination was carried out on the C18 water column condensate (250 x 4.6 mm, particle size 5 µm). The mobile phase consisted of a mixture of 0.5 mM potassium orthophosphate hydrogen buffer: methanol in the ratio of 55:45 v / v, pH 5.3 was adjusted with HCl and the flow of the mobile phase was maintained at 1 ml / min. As a result of the chromatographic analysis, the drugs were separated and the retention times of ertugliflozin and sitagliptin were 2.39 and 4.60 min. The method offers an option for fast and accurate determination of drugs in the combination. The method developed was also validated according to the ICH guidelines and the calibration curve was linear and the value of the regression coefficient (R 2) was 0.999 and the concentration ranged between 37.5-112.5 and 250-750. µg / mL for ertugliflozin and sitagliptin, respectively. The limit of quantification and the limit of detection of the method were found 0.1 and 0.3 µg / mL

and 0.4 and 1 µg / mL for Ertugliflozin and Sitagliptin.[27]

In a research, Rao et al., (2019) performed a high performance liquid chromatography (HPLC) method for the simultaneous estimation of metformin hydrochloride and ertugliflozin in the pharmaceutical formulation. According to analytical conditions Column C8 (150 mm × 4.6 mm, 5 µm) at room temperature. As mobile phase, phosphate buffer: acetonitrile was used in the ratio 55:45 v / v. The flow rate was maintained at 1.0 ml / min and the analysis was performed at 224 nm. The method was linear in the concentration range from 125 to 750 µg / mL and from 1.875 to 11.25 µg / mL for metformin hydrochloride and ertugliflozin with a regression coefficient r2 = 0.999. The method was found to be accurate with a percentage relative standard deviation of less than 2%. The recovery rate of the developed method was 100.15%. A simple, accurate, accurate, and less time-consuming reverse phase HPLC method has been developed and validated for the simultaneous estimation of metformin hydrochloride and ertugliflozin, according to the ICH28 guidelines.

In a survey provided by Laxmi et al., (2019) an analytical method on high performance reverse phase liquid chromatography with PDA detection method for the simultaneous determination of ertugliflozin and sitagliptin in bulk and in their tablets. The separation and assay of ertugliflozin and sitagliptin was performed using the Cosmicsil C8 column (250mm x 4.6mm ID, 5 µm particle size) in isocratic elution mode. The optimized mobile phase was 0.1 molar dipotassium hydrogen phosphate and methanol (65:35, v / v). The eluted analytes are monitored at a wavelength of 225 nm. The method separated ertugliflozin and sitagliptin over a 7 minute analysis time. The linearity of ertugliflozin and sitagliptin was in the concentration range of 7.5-22.50 µg / mL and 50-150 µg / mL, respectively, by method. The developed method was evaluated by analyzing sitagliptin and ertugliflozin in the available tablet form. The percentage recoveries (± RSD) were 99.60 ± 0.027 and 99.83 ± 0.017 for sitagliptin and ertugliflozin, respectively. The results demonstrated the non-interference of the tablet excipients with good recovery and precision. Therefore, the method for routine quality control testing of sitagliptin and ertugliflozin can be suggested.[29]

Han et al., (2019) developed a novel bioanalytical method using high performance liquid chromatography (HPLC) in conjunction with fluorescence detection for the quantitative determination of ERTU in rat plasma. The acetonitrile-based protein precipitation method was used for sample preparation and the chromatographic separation was performed on a Kinetex® C18 column with an isocratic mobile phase comprising acetonitrile and 10 mM potassium phosphate buffer (pH 6, 0). The eluent was monitored by a fluorescence detector at an optimized pair of excitation / emission wavelengths of 277/320 nm.[30]

In another investigation by Anjali et al., (2019) a simple, accurate and precise method was developed for the simultaneous estimation of Sitagliptin and Ertugliflozin in tablet dosage form. The method consisted of solving simultaneous equations (Vierodt method), based on the measurement of absorbance at two wavelengths, 210 nm and 221 nm, which were the λmax values of SGT and ETR, respectively, in a mixture of buffer of 0.1% OPA and acetonitrile. Both SGT and ETR showed linearity in all selected wavelengths and respected the beer law in the concentration range of 7.0 to 42 µg / ml and 4.2 to 6.3 µg / ml, respectively. 210 nm and 221 nm. Recovery studies were performed for SGT and TRUS, and the recovery rate for both drugs was in the range of 100.34 to 99.95%, respectively.[31]

CONCLUSION

SGLT2 inhibitors are also known as gliflozins. These drugs inhibit the re-absorption of glucose from the blood that is filtered through the kidneys and therefore lower blood sugar by facilitating glucose excretion in urine. They act by inhibiting sodium-glucose transport protein 2 (SGLT2).

To date, the US FDA has approved four types of SGLT2 inhibitors to treat diabetes mellitus II: Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin. Table 2 summarizes various HPLC methods developed for the determination of this class of antidiabetic drugs.

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