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A REVIEW ON ANALYTICAL METHODS USED IN SGLT2 INHIBITOR (EMPAGLIFLOZIN)

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ABSTRACT

This study looks into empagliflozin, a novel type of diabetes drug called sodium–glucose co transporter blockers (SGLTi), as well as its analytical technique. Diabetes is one of the oldest diseases known to man. There are 4 different types of diabetes mellitus: prediabetes, gestational, type 1 diabetes, and type 2 diabetes. Type 2 diabetes was previously known as non-insulin-dependent diabetes or adult-onset diabetes. In persons with type 2 diabetes and existing cardiovascular disease, empagliflozin was the first SGLT2-inhibitor medication to decrease the risk of cardiovascular risk.In terms of pharmacokinetics, Empagliflozin has been rapidly absorbed from the gastrointestinal tract, reaching c max after 1.33–3.0 h and then decreasing in a biphasic fashion, with a mean t12 ranging from 10.3 to 18.8 h, half life(t12) was up to 13.1 h, AUC but also c peak seem to be 89.8 and 70.7, CLR around 72 h varied from 32.1 to 51.3 mL/min, urinalysis (fe) over 72 HPLC-based analytical technique invention, testing of Durability Displaying RP-HPLC,UV,RP-LC.UPLC method with some other pharmaceuticals are among the analytical techniques used in empagliflozin. Empagliflozin has been used in individuals with cardiac arrest to lower the risk of hospitalization and mortality from heart failure.

Keywords: Type 2 diabetes (T2D), empagliflozin, pharmacokinetic and pharmacodynamics, RP-HPLC, UV UPLC

INTRODUCTION:

Diabetes is one of the oldest diseases known to man. It was first inscribed on an Egyptian papyrus about 3000 years ago **[1]**. Diabetes mellitus is a multisystemic chronic illness that causes microvascular and macrovascular problems. Diabetes now affects 6.4 percent of the global population and is anticipated to rise to 7.7 percent by 2030 **[2]**. There are four different kinds of diabetes mellitus: prediabetes, gestational, type 1 diabetes, and type 2 diabetes. Type 2 diabetes was previously known as non-insulin-dependent diabetes or adult-onset mellitus **[3]**. The leading cause of disease and mortality in people with type 2 diabetes is cardiovascular disease **[4]**. To reduce the risk of problems, glucose and lipid concentrations, as well as blood pressure, must be closely monitored **[5]**.Increased hyperinsulinemia, insulin resistance, and pancreatic-cell failure characterise T2D, with up to 50% loss of tissue at diagnosis **[6]**. Patients (10–17 years old) lose -cells more quickly, which might explain why patients identified at a young age have a higher rate of therapy failure **[7]**. This study looks into empagliflozin, a novel type of diabetic drug known as sodium–glucose co transporter blockers (SGLTi), as well as its analytical technique. The glucose transporters sodium glucose co transporter blockers 1 and 2 reabsorbed glucose from the glomeruli. These two carriers reabsorb the bulk of a substantial load of filter glucose, on the range of 180 grams glucose per day, resulting in less than 0.5 g glucose per day being wasted in the urine **[8]**. SGLT2 is the major glucose exporter, providing for 90percent of glucose uptake and becoming saturated only when glucose concentrations above 35 mM **[9, 10]**. SGLT1 is involved primarily in glucose uptake from the stomach and is found in the intestine and kidneys. SGLT2i are novel anti-diabetic drugs that work by preventing reabsorption of glucose in the proximal convoluted tubule and promoting glycosuria, reducing plasma glucose levels and raising glycosuria **[11]**. Empagliflozin is just an SGLT2 blocker that has been authorised and for treatment of people in T2D in the European Union, the United States, and Japanese, among other places. Empaglifozin demonstrated cardioprotective and renoprotective effects in patients with T2D and developed CVD in the Phase 3 Level of studies, a landmark (CVOT); the benefcial effects on cardiac (CV) incidents therefore in community are curiosity in the accepted identifying for the drug in the Usa and The eu **[12]**.

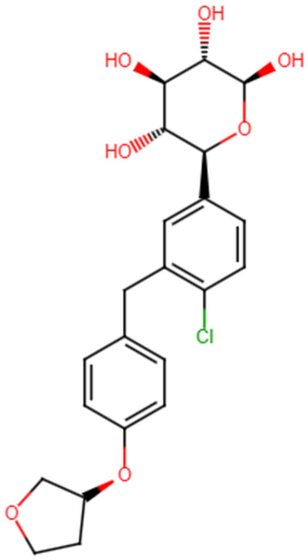

Figure:1 Structure of Empagliflozin

Mechanism of action:

Empagliflozin lowers glomerular glucose absorption and increases urine excretion of glucose by inhibiting (SGLT-2) located in the proximal convoluted tubule of the kidneys. The medication has a glucose-lowering action that is not dependent on insulin. Bladder glucose output increased by approximately 64 g/day in type 2 diabetic individuals using 10 mg of empagliflozin and 78 g/day in those taking 25 mg. Empagliflozin decreases salt and volume load by acting as a diuretic and natriuretic, promoting intravascular contraction and lowering blood pressure without raising heart rate **[13]**.

Pharmacokinetic and pharmacodynamics:

Empagliflozin was promptly absorbed after oral treatment and demonstrated a biphasic reduction in fit people in one oral dosages (0.5–800 mg) research. The median time to achieve maximum concentration (time maximum) was 1.5 to 2.1 hours, while the terminal elimination time (t12) was up to 13.1 hours. Both mean AUC and Cmax were lower under fed settings than when the medication was administered fasted: the arithmetic mean ratios (GMR; percent) and 90 % confidence interval (CI) for AUC and Cmax, respectively, was 89.8 (84.5–95.5) as well as 70.7 (61.0–81.8), respectively. The total percent of empagliflozin excreted by the kidneys (fe) over 72 hours varied from 11.0 to 18.7%, while absolute bioavailability (CLR) over 72 hours range from 32.1 to 51.3 mL/min. Plasma level of empagliflozin below the lower LOQ [lower limit for plasma 1.11 nmol/L (0.5 ng/mL)] were generally detectable for 72 hours at higher doses below 100 mg, but after 24 hours at the 0.5 mg

dose, plasma concentrations of empagliflozin were below the LLOQ[lower limit for plasma 1.11 nmol/L (0.5 ng/mL)]. The maximal UGE was 90.8 g, happening at the 400 mg dosage, 24 hours following oral administration of empagliflozin.At single daily dosages of 0.5–10 mg, empagliflozin prevented reabsorption of 40 percent of filtered glucose, increasing to 40–60 percentage inhibition of filtering glucose at larger doses, and plateauing at the 100 mg dose. Over 72 hours, the total level of glucose excreted was dosage proportionate, with a plateau around the 100 milligramme. In all dosing groups, the time to maximal UGE rate was identical (approximately 7 h). When empagliflozin was given with food, it had no effect on UGE **[14]**. Within oral treatment, empagliflozin was quickly absorbed, attaining Cmax upon 1.33–3.0 h and thereafter falling in a biphasic way, with a mean t12 spanning between 10.3 to 18.8 h. Following numerous oral doses, increase in exposure were dosage proportionate **[15, 16]**.

Analytical methods used in empagliflozin:

Anas M. Hanif, RabiaBushra- Development and use of an HPLC-based analytical technique for empagliflozin.

The current study is predicated on developing effective methods for quantifying empagliflozin in crude and pharmaceutical dose forms, as there is currently no pharmacopoeial approach for the medication. According to ICH requirements, the devised analytical technique was verified. For drug analysis, a C18 column containing 0.1 percent trifluoroacetic acid & acetonitrile (70:30 v/v) mobile phase (pH 4.8) was utilised. Over the concentration range of 0.025-30 g mL-1, the calibration plot revealed strong linear regression (r 2>0.999). The LOD and LOQ, respectively, were determined to be 0.020 µg mL-1 and 0.061 g mL-1.The recovery rate was predicted to be between 98.0 and 100.13 percent. The precision and accuracy data were determined to be quite than 2%, indicating that the technology is suitable for regular analysis in the pharmaceutical industry. Furthermore, with a mean percent accuracy of >98%, the medication solution was shown to be stable in the refrigerator and at room temperature. Using this newly discovered technology, the contents of empagliflozin were assessed in both the crude API and commercial tablet brands. Pure empagliflozin and tablet products had mean assays that varied from 99.29 percent 1.12 to 100.95 percent 1.69, and 97.18 percent 1.59 to 98.92 percent 1.00, respectively. Based on these results, the current method is appropriate for measuring

empagliflozin in both raw and prescription dose forms **[17]**.

Sushil D. Patil- he explore the development and validation of an empagliflozin stability indicating RP-HPLC method

A RP Stability Indicator Using a Phenomenex carbon 18 column (25 cm 4.6 mm, 5m) and a mobile phase mixture Methanol: Water (70:30 percent v/v), an HPLC technique for the detection of Empagliflozin was developed and validated. Eluent was identified at 224 nm at a steady flow rate of 1.0 mL/min. Linearity was discovered in the concentration range 2-14 g/mL (R2=0.999) using regression in calibration curve investigations. Alkaline, acidic, oxidation, moist heat, thermal degradation, and photolysis were all used to stress empagliflozin. Empagliflozin is more acid-sensitive than other drugs. At the retention period of Empagliflozin, there was no influence from excipients or degradation products, supporting the method's specificity **[18]**.

Manojkumar K. Munde-he did Analytical Method for Metformin HCl and Empagliflozin using UV Spectroscopy

Simultaneous estimate of Empagliflozin and Metformin hcl in bulk and tablet formulations was devised and verified using four novel UV spectrophotometric methods: concurrent formula, absorbance ratio, AUC, and its first derivative (zero crossing). Both medicines' absorbance was read at 224 and 232 nm using the simultaneous equation approach. The absorbance ratio technique was used to measure empagliflozin and metformin hcl at 224 and 232 nm. Both medications were measured around 224 and 232 nanometer using the area under the curve approach. The first derivative (0 crossing) technique for Metformin hcl and Empagliflozin was based on converting Ultraviolet spectra into the first derivative spectra, then measuring 1st derivative wavelength at 224 & 232 nanometer, accordingly, used 2 nanometers as wavelength gap and 1 as scaling factor. The procedures were found to be simple, quick, highly sensitive, and cost-effective, and hence may be utilised for routine QC analysis of Empagliflozin and Metformin hcl on market tablet dosage form **[19]**.

Geethasusmita A- RP HPLC technique for the simultaneous measurement of MET and EMP in tablet dosage form.

For the detection of metformin and empagliflozin, a quick reverse-phase liquid chromatography technique was devised using multiple ratios of mobile phases, varied chromatographic settings, and flow rates.

Satisfactory results were achieved using the appropriate mobile phase (buffer:acetonitrile) ratio of 50:50, BDS 250 mm4.6 mm, 5 m particle size column, and 1 ml/min flow rate. Metformin had a retention duration of 2.588 minutes while empagliflozin had a retention time of 3.679 minutes. The stability studies criteria, plate count, & tailing factor were all within the acceptable ranges, and the analyte peaks had high resolution. There was no different of excipients and MP with the analyte peaks that imply the method is specific. The approach demonstrated linearity between metformin concentrations of 0–1275 (ug/ml) and empagliflozin concentrations of 0–7.5 (ug/ml). Metformin's regression equation was y=9334.0 x+593.4, whereas empagliflozin's was y=48830 x+914.1. Over a large range, the calibration plot shows a linear connection among peak area and concentration. For metformin and empagliflozin, the % recoveries were 100.01 percent and 100.65 percent, respectively. The approach was robust, as evidenced by minor differences in the analytical findings when the flow, solvent mixture, and temperature were changed. In metformin and empagliflozin, the limit of detection were 0.10 ug/ml and 0.31 ug/ml, respectively. The quantification results' limits were 0.01 ug/ml and 0.03 ug/ml, correspondingly, demonstrating that the technique proposed is sensitive **[20]**.

Usmangani K. Chhalotiya-The RP–LC technique was used to quantify EMP, LIN, and MET hcl in mass and synthetic mixtures.

For simultaneous quantification of Empaglifozin, Linagliptin, and Metformin Hydrochloride in bulk and synthetic mixtures, a simple, sensitive, specific, precise, and accurate (RP- HPLC) approach has been established. Carbon 18 column (250 mm4.6 mm, 5 m) was used as the stationary phase for isocratic elution with Solvent: Water:Methanol in a ratios of (27: 53: 20, v/v/v) pH 4 adjusted with one percent Ortho-H_3PO_4as the mobile phase at a flow rate of one ml/min. At a common wavelength of 223 nm, a PDA detector was utilised to analyse all three medications simultaneously, and that each sample volume was 20 l. Empaglifozin, Linagliptin, and Metformin HCl have linear ranges of 0.5–5 g/ml, 0.25–2.5 g/ml, and 50–500 g/ml, respectively. Empaglifozin, Linagliptin, and Metformin Hydrochloride showed retention times of 14.5 minutes, 3.4 minutes, and 2.01 minutes, respectively. Empaglifozin, Linagliptin, and Metformin Hydrochloride showed percentage recovery for 99.98–100.81 percent, 99.33–

100.57 percent, and 100.65–101.35 percent, respectively **[21]**.

Bassam M. Ayoub-UPLC determination of empagliflozin, linagliptin and metformin in simultaneously

The first UPLC approach for testing EMP, LIN and MET hcl in various pharmaceutical formulations was developed. Chromatographic separation was achieved on a C18 column (100 mm 2.1 micrometres, 2.2 m) (50: 50, v/v) using isocratic elution with buffer pH (4) with methanol as the mobile phase. Linearity, accuracy, and precision were found to be good for empagliflozin, and metformin hcl and linagliptin over concentration ranges of one to thirty two grams/ mL1, zero point five to sixteen grams/ mL1, and one to hundred grams/ mL1 respectively.Tooptimise the chromatographic conditions, all factors were investigated. The improved approach was evaluated and found suitable for product testing of the medications specified in their various pharmaceutical dose forms **[22]**.

Krishna Rao Vankalapati, SathyanarayanaBoodida-UPLC Method for Combined Estimation of Met, Lin, and Emp anti diabetes drug in Bulk and Pharmaceutical Dosage Form

Using a C18 column (2.1 x 50 mm, 1.8m) as a stationary phase and a PO_4^{3-} buffer (pH 3) 40 percent & 60percent acetonitrile as mobile phase flow of 0.6 mL/min, a fast stability-indicating RP-UPLC was advanced and evaluated for the prediction of Metformin, Linagliptin , and Empagliflozin. A photodiode detector was used to detect the light at 248 nm. The linear, sensitivity, selectivity, ruggedness, specificity, precision, and accuracy of the system were investigated. Over the range of concentrations of 50-150 g/mL (Metformin), 5-15 g/mL (Linagliptin), and 10-30 g/mL (Empagliflozin), the peaked area response-concentration slope was rectilinear, with quantitation limitations of 0.042 g/mL (Metformin), 0.023 g/mL (Linagliptin), and 0.059 g/mL (E (Empagliflozin).The suggested approach was validated for the simultaneous measurement of Metformin, Linagliptin, and Empagliflozin in combination tablet dose form. The suggested approach was shown to be faster and less expensive than previously reported RP-UPLC methods. For QC and drug analysis, the designed and verified stability-indicating RP-UPLC technique proved suitable **[23]**.

Nenavathpadmaja and Guttenaveerabhadram- Met and Emp in Bulk and Tablet Solid Dosage form: Rp-Uplc-Dad

The goal of this study was to create and test a new stability-indicating RP-UPLC-DAD technique for the simultaneous determination of Metformin and Empagliflozin in mass and tablets dose forms. With retention duration, solvent consumption, resolution, and lower cost, this innovative RP-UPLC technique outperforms conventional Reverse phase-HPLC in terms of technology. A Waters design UPLC machine with a PDA detector &autosampler was used to separate the peak areas.All analytes were separated using a mobile phase containing point one percent ortho H_3PO_4 buffer (pH 3.4 with 0.1 N NaoH) and methanol in the ratio 40:60 percent v/v through the C18 BEH UPLC (100mm x 2.1mm,1.8m) at 350 c Column temp and the detector wavelength was set at 254 nm. Two medications' tailing factor, resolution, and plate count in the system were 1.16, 1.37, 3.47, 2314.34, and 4723, respectively. Metformin and Empagliflozin had retention times and peak areas of 0.882 and 3.471, 4887835 and 163463, respectively.Metformin and Empagliflozin have value more than 0.999 in the regression equation. Met and Emphad a percent recovery of 99.92 % -100.12 % and 100.12 % -100.56 %, respectively. Metformin and Empagliflozin both were tested under stress conditions including such acidic, basic, oxidative, thermal, and photo degradation, but acid experiments revealed significant deterioration. The system parameters are validated with newly designed RP-UPLC-DAD chromatographic method **[24]**.

RazanA.ahmad, Waelabudayyih *et al*. Development of an RP HPLC technique for estimating metformin, empagliflozin, and pioglitazone in bulk and tablet dose forms.

Anti-diabetic medicines such as empagliflozin, pioglitazone, and metformin are used alone or in combination to treat diabetes. To test these medications in bulk and tablet dosage forms, a cost-effective, easy, accurate, specific, and stability-indicating RP-HPLC technique has been developed and validated. The separating of the medicines was done according to ICH recommendations, with a mobile phase made up of h3po4 buffer with acetonitrile (30:70 v/v) set to pH 2.7.An C18 column – (250 mm x 4.6 mm), 5 µm at a flow rate of 0.5 ml/min at 25°C, & sensing supervised at 230 nm were used. In the 20-250 ppm range, the R2 was just not 0.9998. Drugs were evaluated for stability under a variety of stress conditions, including basic, acidic, neutral, oxidation, and heat deterioration.The results were checked for detection limits, quantification limits, accuracy, precision, and

linearity. Variations in pH of the solvent system, detector wavelength, temp, & mobile phase composition did not impact the approach. Empagliflozin, metformin, and pioglitazone had retention times of 3.2 minutes, 2 minutes, and 2.6 minutes, respectively, with a runtime of 7 minutes. At 10–100 ppm, detector linearity was achieved, with correlation coefficients of 0.9994, 0.9993, and 0.9998, respectively, with empagliflozin, pioglitazone, and metformin. The methods relatively low standard deviation, i.e. 2%, verified findings, and high recovery percent attest to its applicability for rapid screening of bulk and tablets comprising these medicines in pharmaceutical formulations **[25]**.

CONCLUSION:

In persons with type 2 diabetes and existing cardiovascular disease, empagliflozin was the first SGLT2-inhibitor medication to minimize the risk of cardiovascular death. Empagliflozin is sometimes used in combination with other drugs to help patients with T2D manage their blood glucose levels. Empagliflozin is used to lower the risk of stroke, cardiac arrest, and mortality in persons with type 2 diabetes who also have heart or blood vessel disease. Empagliflozin can also be used to lower the risk of having to be hospitalised and mortality from heart and blood disease in persons with heart failure. It helps to reduce blood sugar levels by helping the kidneys to excrete more blood sugar in the urine. T1D and diabetic ketoacidosis are not treated with empagliflozin.

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Conflict of interest:

The authors declare that No conflict of interest among us

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