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REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF EMPAGLIFLOZIN

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ABSTRACT

Antidiabetic medicines treat diabetes mellitus by reducing blood glucose levels. Antidiabetic medicines are primarily classified as oral hypoglycemic agents and insulin preparations. Empagliflozin is an oral hypoglycemic agent. Empagliflozin is an SGLT 2 inhibitor, a kind of diabetes drug that targets transporters in the kidney's proximal tubules to reduce blood glucose levels by increasing glucosuria. It includes information on the development of several analytical methods such as UV, HPLC, HPTLC, and QbD-based HPLC methods, allowing us to employ any method for further study of Empagliflozin.

KEYWORDS: Analytical methods, Type 2 diabetes, SGLT 2 inhibitors, Antidiabetics, Empagliflozin.

INTRODUCTION

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. In the past three decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival.[1]

There are three major types of diabetes: (1) Type 1, in which the pancreas does not produce insulin; (b) type 2 in which the body cells are resistant to the action of insulin that is being produced and over time the production of insulin progressively decreases; and (c) gestational diabetes which occurs in pregnancy and can cause some complications during the pregnancy, and at birth and increases the risk of type 2 diabetes in the mother and obesity in the offspring.

In addition, there are two other categories of glucose intolerance - impaired fasting glucose (IFG) and impaired fasting glycemia (IGT) that are intermediate conditions between normal and diabetic blood glucose levels, although the transition is not inevitable. People with IFG and IGT are at increased risk of CVD than people with normal blood glucose values. [2]

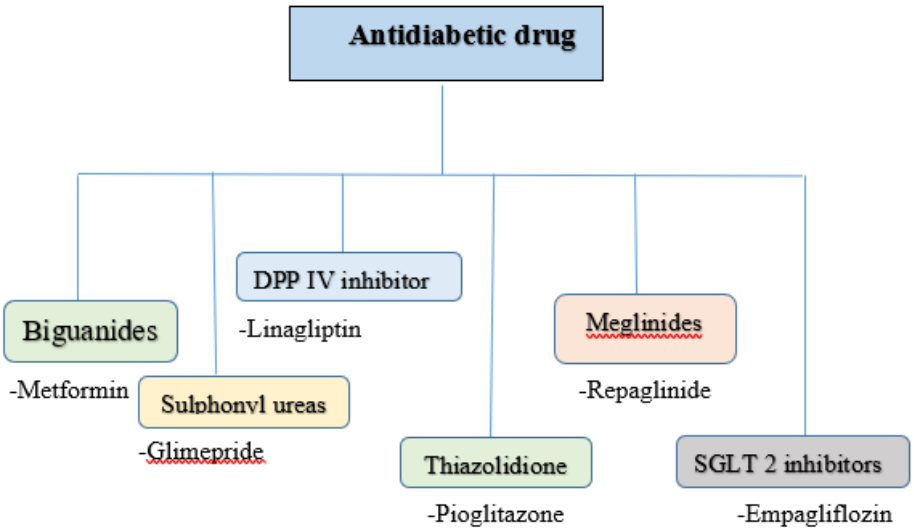

Figure 1: Classification of Antidiabetic Drug

SGLT 2 inhibitors

SGLT 2 inhibitors are class of oral diabetes drugs. commonly used for patient with type 2 diabetes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class of oral (taken by mouth) prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes.[3]

SGLT2 inhibitors, which are also called gliflozins, are a class of drugs that lower your blood sugar levels by preventing your kidneys from reabsorbing sugar that is created by your body and the extra sugar leaves through in your urine.

Sodium glucose cotransporter-2 inhibitors are an established class of drugs which act to decrease blood glucose by preventing reabsorption of glucose, mainly from proximal renal tubule in the kidney. Glucose is therefore lost in urine, decreasing the blood glucose level. The osmotic effect of the glucose loss leads to diuresis and a drop in blood pressure. These agents act selectively on SGLT-2 receptors (found in kidneys) but may also interact with SGLT-1 receptors which are in the gastrointestinal tract and proximal renal tubules. These drugs are currently licensed and used widely in people with type 2 diabetes and have shown significant cardiovascular and kidney benefits in different subsets of this group of people.[3,4]

Examples of SGLT 2 inhibitors are Bexagliflоxin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin.

Empagliflozin

Empagliflozin is an inhibitor of sodium-glucose co-transporter-2 (SGLT2), the transporters primarily responsible for the reabsorption of glucose in the kidney.[5]

It is used clinically as an adjunct to diet and exercise, often in combination with other drug therapies for the management of type 2 diabetes mellitus.[6]

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 centre. Pubchem was discovered and developed by Boehringer-Ingelheim. It was approved by the FDA in 2014 and is marketed in four formulations: Jardiance (empagliflozin), Glyxambi (empagliflozin and linagliptin), Synjardy (empagliflozin and metformin) and Synjardy XR (empagliflozin and metformin extended-release).[7]

Mechanism of action

The vast majority of glucose filtered through the glomerulus is reabsorbed within the proximal tubule, primarily via SGLT2 (sodium-glucose linked co-transporter-2) which is responsible for ~90% of the total glucose reabsorption within the kidneys. Na^+/K^+-ATPase on the basolateral membrane of proximal tubular cells utilize ATP to actively pump Na+ ions into the interstitial surrounding the tubule, establishing a Na^+ gradient within the tubular cell. SGLT2 on the apical membrane of these cells then utilize this gradient to facilitate secondary active co-transport of both Na+ and glucose out of the filtrate, thereby reabsorbing glucose back into the blood – inhibiting this co-transport, then, allows for a marked increase in

glucosuria and decrease in blood glucose levels. Empagliflozin is a potent inhibitor of renal SGLT2 transporters located in the proximal tubules of the kidneys and works to lower blood glucose levels via an increase in glucosuria.[8]

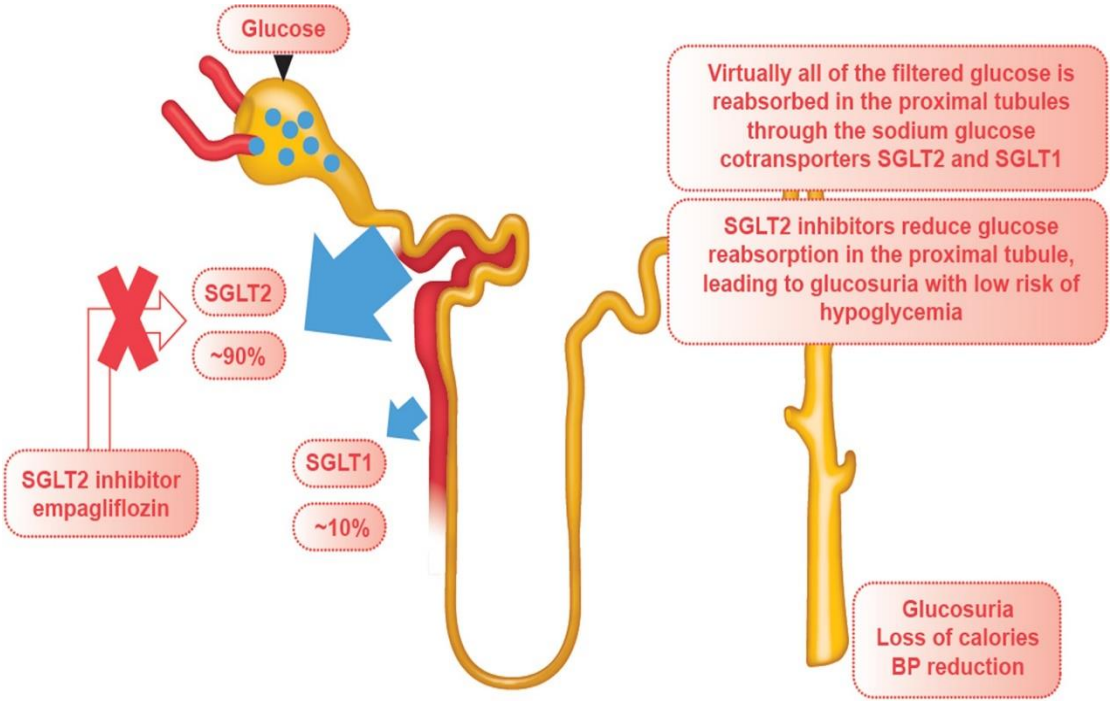

Figure 2: Mechanism of Empagliflozin.

Chemistry of Empagliflozin is 4 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yl oxy)-benzyl]-benzene.[9] [Fig.3] Its chemical formula isC23H27ClO7.[6] It is a novel molecule with molecular weight 450.91g/mol. The partition co-efficient(log p) is 1.7.while Dissociation constant is 12.57.The appearance is White and melting point is 151 - 153°C.[8]

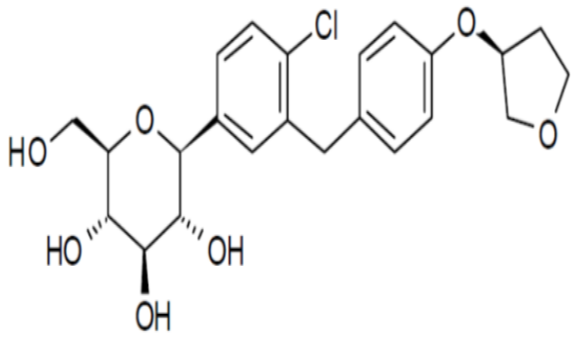

Figure 3: Structure of Empagliflozin.

Pharmacokinetics

Absorption: Oral administration, peak plasma concentrations are reached in approximately 1.5 hours (tmax). at steady-state, plasma auc and cmax were 1870 nmol·h/l and 259 nmol/l, respectively, following therapy with Empagliflozin 10mg daily and 4740 nmol·h/l and 687 nmol/l, respectively. therapy with Empagliflozin 25mg daily.18 administration with food does not significantly affect the absorption of Empagliflozin.

Distribution: The apparent steady-state volume of distribution was estimated to be 73.8 L, based on a population pharmacokinetic analysis. administration of an oral [14C]-Empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism: No major metabolites of Empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-Oglucuronide). Systemic exposure of each metabolite was less than 10% of total drugrelated material. In vitro studies suggested that the primary route of metabolism of Empagliflozin in humans is glucuronidation by the uridine 5'-diphosphoglucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination: The apparent terminal elimination half-life of Empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for Empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once-daily dosing, steady-state plasma concentrations of Empagliflozin were reached by the fifth dose. Consistent with half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [14C]- Empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Administration

Empagliflozin is an oral medication dosed at either 10 mg daily or 25 mg daily. The recommended dose is 10 mg once daily in the morning, taken with or without food. If tolerated initially, dosing may increase up to 25 mg. correct volume depletion, if present, before starting the drug.[10]

Therapeutic Indication

- Empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in patients aged 10 years and older with type 2 diabetes. It is used either alone or in combination with metformin or linagliptin.
- It is also indicated to reduce the risk of cardiovascular death in adult patients with both type 2 diabetes mellitus and established cardiovascular disease, either alone or as a combination product with metformin.

Contraindication

- The use of empagliflozin is not recommended if GFR is less than 45 mL/min or during the second and third trimesters of pregnancy.
- Other contraindications include those with end-stage renal disease, those on dialysis, and those with a severe hypersensitivity reaction to empagliflozin. Empagliflozin may be used in cases of hepatic impairment.
- Empagliflozin is not for use with patients with Type 1 diabetes or those with diabetic ketoacidosis.

Side effects

Empagliflozin has several adverse effects to be of note, including hypotension, ketoacidosis, acute kidney injury, genital mycotic infections, hypoglycemia when used with insulin, dyslipidemia, Fournier gangrene, and pyelonephritis.

Toxicity

- The most commonly reported side effects were urinary tract infections, genital mycotic infections, and dyslipidemia. Due to its diuretic properties related to volume depletion, there were also reports of dehydration, hypotension, hypovolemia, and syncope.
- The FDA issued a warning for Fournier gangrene, a type of necrotizing fasciitis of the perineum. There were twelve reported cases, and all twelve were hospitalized, requiring surgical debridement. If suspected, stop the drug and have the patient report to the ED promptly for a surgical evaluation.

USE

Empagliflozin is used to treat type 2 diabetes. It works in the kidneys to prevent absorption of glucose (blood sugar). This helps lower the blood sugar level. Empagliflozin does not help patients who have insulin-dependent or type 1 diabetes.

Reported Methods for Assessment of Empagliflozin

Sr. No.	Title	Description	Ref. No.
UV-Spectrophotometric method			
1.	Development and validation of simple **UV-Spectrophotometric** method for the determination of Empagliflozin	**Solvent:** Water: Methanol (9.0:1.0%v/v) **Wavelength:** 224 nm **Linearity:** 1.0–3.0 µg/mL **R^2:** 0.998	[11]
2.	Method development and validation of Empagliflozin in bulk and pharmaceutical dosage form using **UV spectroscopy**	**Solvent:** Ethanol and Water **Wavelength:** 223 nm **Linearity:** 1-30µg/mL **R^2**:0.997	[12]
Reverse Phase High Performance Liquid Chromatography(RP-HPLC)			
3.	**RP-HPLC** method for quantification of Empagliflozin in pharmaceutical formulation	**Stationary phase:** C_{18}G column (250 x 4.6 mm, 5µm) **Mobile Phase:** Methanol :Water (70: 30% v/v) **Linearity:** 10–90 µg/mL **Flowrate:** 1 mL/min	[13]
4.	Development and validation of stability Indicating **RP-HPLC** method for Empagliflozin	**Stationary phase:** Phenomenex C_{18} column (250 x 4.6 mm, 5µm) **Mobile Phase:** Methanol: Water (70: 30% v/v) **Linearity:** 2–14 µg/mL **Flowrate:** 1.0 mL/min	[14]
5.	Empagliflozin: **HPLC** based analytical method development and application to pharmaceutical raw material and dosage form	**Stationary phase:** C_{18} column (250 x 4.6 mm, 5µm) **Mobile Phase:** Water: Acetonitrile (70:30 %v/v):0.1% Trifluoroacetic acid solution (pH 4.8) **Linearity :** 0.025-30 µg mL **Flow rate :** 1.0 mL/ min	[15]
6.	A new simple method development, validation and forced degradation studies of Empagliflozin by using **RP-HPLC**	**Stationary phase:** Develosil ODS HG-5 RP C_{18} column (150 x 4.6mm,5µm) **Mobile Phase:** Water : Acetonitrile (45:55%v/v) Phosphate Buffer (pH-2.8) **Flow rate :** 1.0 mL/ min **Linearity:** 0–50 µg/mL	[16]
High-Performance Thin Layer Chromatography(HPTLC)			
7.	A novel validated stability indicating method for quantification of Empagliflozin in bulk and marketed formulation by **HPTLC** applying experimental design approach**.**	**Stationary phase:** Aluminum plate that had previously been coated with silica gel **Mobile Phase:** Ammonium acetate (2%):Triethylamine : Isopropyl alcohol (4:1:5 %v/v/v) **Detection:** 237 nm	[17]

Quality by Design(QbD)			
8.	The application of **quality by design** in the development of the liquid chromatography method to determine Empagliflozin in the presence of its organic impurities	**Stationary phase:** C_{18} column (250x 4.6mm, 5µm) **Mobile phase:** Acetonitrile :water (72:28%v/v) **Detection:** 230 nm	[18]

CONCLUSION

Empagliflozin is a strong SGLT2 inhibitor. Empagliflozin's mode of action, which involves preventing glucose reabsorption in proximal tubules, allows it to provide a variety of advantages in addition to glucosuria and normoglycemia. Although empagliflozin has many benefits, it also has a number of side effects, the most notable of which are troublesome genital fungal infections and urinary tract infections, symptomatic hypotension, a risk of hypoglycemia when combined with insulin or insulin-secreting drugs, and rare ketosis. In addition to treating T2DM, the review paper included a summary of the analytical procedure for Empagliflozin. As a result, just one analytical technique for Empagliflozin is accessible in this review article. We can use any approach to do deeper investigation of Empagliflozin.

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