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Review Article

Review on SGLT2 Inhibitors

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A B S T R A C T

The pharmaceutical industry employs a variety of analytical techniques to test the quality, concentration, and composition of medicines in biological fluids. This review work to provide the most existing analytical methods for the analysis of SGLT2 inhibitors (Empagliflozin, Dapagliflozin, Canagliflozin) in active pharmaceutical ingredients, biological fluids & pharmaceutical dosage forms. SGLT2 inhibitors are gliflozin derivatives, used generally in the treatment of type 2 diabetes mellitus. These inhibitors have pharmacological action in the kidneys, where they filter and reabsorb glucose in the proximal convoluted tubule and help to contribute to glucose homeostasis. The analytical techniques such as HPLC, LC-MS/MS, Mass spectrometry, UV-spectroscopy, and HPTLC on selected SGLT2 inhibitors were reviewed.

Keywords: - Analytical techniques, biological fluids, Diabetes mellitus, SGLT2 Inhibitors

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INTRODUCTION

Diabetes mellitus is a chronic disorder of carbohydrates, fats and protein metabolism.[1]diabetes impairs the body's capacity to utilize food because either the pancreas does not produce sufficient insulin or the body does not utilize insulin efficiently.[2]Diabetes mellitus (DM) is a long-term metabolic disease caused by a complex interaction between insulin resistance and insulin deficiency. As either a result, the proximal components (carbohydrates, proteins, and lipids) are utilized and deposited in an unorganized manner, and the quantity of adenosine triphosphate released is reduced (ATP).

Diabetes mellitus is categorized as follow: -

Type 1 Diabetes Mellitus (T1DM): -

This type of disease (TIDM) needs continuous insulin therapy for the patient to survive.

Type 2 Diabetes Mellitus (T2DM): -

This is not an insulin emergency

Type 3 Diabetes Mellitus (T3DM): -

It is associated with several hormonal illnesses, particularly acromegaly, and medications such as glucocorticoids; it normally improves after oral anti-diabetic therapy

Type 4 Diabetes Mellitus (T4DM): -

This must be treated with or without insulin.[3]

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus (T2DM) is defined as a dysfunction of protein, lipid, and carbohydrate metabolism.[4] Maintaining a healthy blood sugar level is the main goal of controlling T2DM[5].About 90% of all people are fat or overweight now at the time of T2D diagnosis, which leads several specialists to assume that the pathogenesis of the disease is induced by diets that involve excessive food consumption associated with decreased energy expenditure[6]. Type 2 diabetes is understood to be caused by at least 8 different pathologic processes, as compared to the earlier assumption that it was just an insulin resistance disorder. These include improper β-cell insulin secretion, abnormal α-cell glucagon production, abnormal incretin effect, peripheral tissue insulin resistance, increased hepatic glucose generation, increased lipolysis, synaptic dysfunction, and irregular renal control of hyperglycemia[7].

SGLT2 INHIBITORS

Sodium-glucose cotransporter Inhibitors: -

In recent times, sodium-glucose cotransporter 2 (SGLT2) inhibitors, a new class of antihyperglycemic medicines, were authorized for Prediabetes.[8]SGLT2, is present in the brush border's apical membrane in renal proximal tubule cell[9].Sodium-glucose cotransporter-inhibitors (SGLTI2) are medications used to cure Type 2 diabetes that drop blood sugar levels. SGLT2 inhibitors restricts glucose absorption from the proximal tubules and collecting ducts, resulting in glycosuria[10]**.**These inhibitors work pharmacologically in the kidneys, filtering and reabsorbing glucose in the peritubular capillaries, which helps to maintain glucose homeostasis. Other benefits included a lower risk of hypoglycaemia, a reduction in calories, and a drop in blood pressure. For patients who have type 2 diabetes, sodium-glucose cotransporter inhibitors (SGLTI2) are essential in the treatment of renal and cardiovascular complications. The FDA and European Medicine Agency have been able to improve the efficiency of sodium-glucose cotransporter inhibitors for diabetes. In medical practice, empagliflozin, dapagliflozin, or canagliflozin are commonly utilized. they belong to the class of gliflozins. It is an oral hypoglycaemic medicine.[11]

EMPAGLIFLOZIN

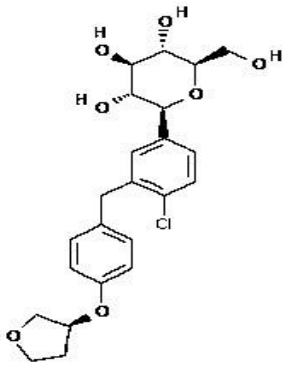
For treatment of type 2 diabetes, empagliflozin (EMPA) is an effective and selective sodium glucose cotransporter 2 (SGLT2) inhibitor. In an insulin-dependent patient, this class lowers plasma glucose levels, and EMPA seems to have the best tolerance for other diabetic medicines in the same class. Empagliflozin is gliflozin derivative.[12]

IUPAC NAME: -

(2S, 3R, 4R, 5S, 6R) -2- [4-chloro -3- [[4-[(3S)-oxolan-3-yl] oxyphenyl] methyl] phenyl]-6(hydroxy methyl) oxane-3, 4, 5-triol

BRAND NAME: - Jardiance

Structure: -



Molecular formula: - $C_{23}H_{27}CLO_7$

Molecular weight: - 450.9g/mol

Mechanism of action: -

Empagliflozin increases glucose elimination in the urine while decreasing renal re - uptake via inhibiting SGLT2. The medication has a glucose-lowering effect without the help of insulin. With 10 mg and 25 mg of empagliflozin, type 2 diabetes patients' urine glucose excretion increased by around 64 grams daily and 78 grams daily, respectively.

Empagliflozin's diuretic characteristics cause intravascular contraction by lowering salt and volume load. additionally, empagliflozin is linked to decreased blood pressure and weight loss without raising the heart rate.[13]

Pharmacokinetics: -

Healthy volunteers and T2DM patients were employed to study the pharmacokinetics of empagliflozin, no clinically major changes were observed between the two groups. Plasma levels of empagliflozin when administered orally were reached 5 minutes well after dose with a 78% bioavailability following that, serum concentrations reduced in a bicontinuous way, with a fast distribution phase and a moderately slow terminal phase.

The steady state mean plasma Area under the curve and Serum creatinine for 10 mg of empagliflozin once daily administration were 1870 nmol h/L and 259 nmol/L, respectively, and 4740 nmol h/L and 687 nmol/L, respectively, for 25 mg of empagliflozin once daily dose. In the effective dose range, empagliflozin's systemic exposure increased in a dose proportional way.[14]

Pharmacodynamics: -

Excretion of urine glucose

Urinary glucose excretion in individuals with type 2 diabetes increase immediately after only single dose with empagliflozin and stayed constant for the duration of a 4-week treatment period, averaging almost 64 g per day with ten mg of empagliflozin and 78 g per day with twenty-five mg of empagliflozin once daily. Over the course of 8 days, normal dose empagliflozin intake produced in an increase in blood - glucose elimination ranging between

77.9 gm with the 10-microgram dose to 89.8gm with the Hundred mg dose.

Cardiac electrophysiology

In a randomized, placebo-controlled, active-comparator, cross-over study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin. Like other SGLT2 inhibitors, empagliflozin lowers serum uric acid levels, probably through an effect on the urate transporter, solute carrier family 2 (facilitated glucose transporter), member 9 (SLC2A9), which is expressed in the proximal convoluted tubule and is involved in the renal handling of urate.[15]

Side Effects: -

Empagliflozin is associated to the following major side effects:

- Hypotension.
- Ketoacidosis.
- Renal function impairment and acute kidney problems.
- Pyelonephritis and uro-sepsis.

- Low blood sugar caused using insulin secretagogues and continuous insulin therapy.
- A high level of lipid from minimal triglyceride. (LDL-C).[16]

Dosage & Administration: -

The starting dose of empaglifozin is 10 mg once day.

Patients who tolerate empaglifozin 10 mg/day may have their dose raised to a maximum of 25 mg/day.[17]

Patients with renal impairment: -

Assessment of renal function is recommended prior to initiation of empagliflozin therapy and periodically thereafter. Empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m2. No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m2. Empagliflozin should be discontinued if eGFR is less than 45 mL/min/1.73 m.2.[18]

Table 1: Analytical methods for determination of empagliflozin

Technique	Extensive method condition	Detection outline	Formulation	Reference
RP-HPLC	**Stationary phase**:-C18 column (250mm×4.6mm,5µm). **Mobile phase**: -Potassium dihydrogen phosphate buffer (pH 3.4) and methanol (70:30v/v). **Linearity**:- 50-150µg/ml	-	Tablets	(19)
LC-MS	**Stationary phase:** Orosil C18 column (150×4.6mm,3µ) **Mobile phase**:-ammonium trifluoroacetate & Methanol (10:90v/v) **Flow rate:-**0.8ml/min.	-	Human dosage form	(20)
UPLC	**Stationary Phase:-**Column:-BEHC18 **Mobile Phase:-**Acetonitrile: phosphate buffer (pH3) (70:30v/v) **Flow Rate;-**0.3ml/min	--	Bulk dosage form	(21)
LC-MS/MS	**Stationary Phase:-** X Bridge C18 column (75mm× 4.6mm,3.5µ) **Mobile phase:** - Acetonitrile, methanol 0.1% v/v formic acid **Flow Rate:-**0.8mL/min **Linearity range:** 2–1000ng/mL	-	Human plasma	(22)
UV-spectroscopy	**Solvent:-**Water, Methanol **Recovery:-99.94**% **LOQ:-**0.111µg/mL **LOD:-**0.036µg/mL	224nm	Bulk Pharmaceutical formulations	(23)
UPLC/DAD (Empagliflozin & three related sub)	**Stationary phase**: - C18column(50 mm×2.1mm 1.7µmparticlesize) **Mobile phase:** Aqueous trifluro acetic acid (0.1% pH2.5) and acetonitrile (60:40) **Flowrate:**0.5ml/min	210nm	Human plasma	(24)
HPLC	**Stationary phase:**C8 column (250mm×4.6mm,5µm) **Mobilephase:**0.1% Ortho phosphoric acid and Acetonitrile (30:70 v/v) **Flow rate:-**1.2ml/min **Temp**:55°C	230nm	Human plasma	(25)
RP-HPLC	**Stationary phase:-**Hypersil bed column150mm x 4.6 mm **Mobile phase: -**(70:30) of 0.1% Orthophosphoric acid and Acetonitrile **Flowrate**:1ml/min **% RSD**:-0.22%	233nm	API	(26)
LC-MS/MS (Empagliflozin And metformin)	**Stationary phase:-**Ethylene Hybrid C18 column (50mm×2.1mm,1.7µm) **Mobile phase:**0.1% Aqueous formic acid: Acetonitrile (75:25,v/v) **Flowrate:** -0.2mLmin^{-1}	-	Pharmaceutical Dosage form	(27)

UPLC (Empaglifozin Linagliiptin and Metformin Hydrochloride)	**Stationary phase:-**C18 column (100mm×2.1 mm,2.2µm) **Mobile phase: -**Potassium dihydrogen phosphate buffer pH (4) -Methanol (50:50, v/v)	-	Pharmaceutical Dosage form	(28)

DAPAGLIFLOZIN: -

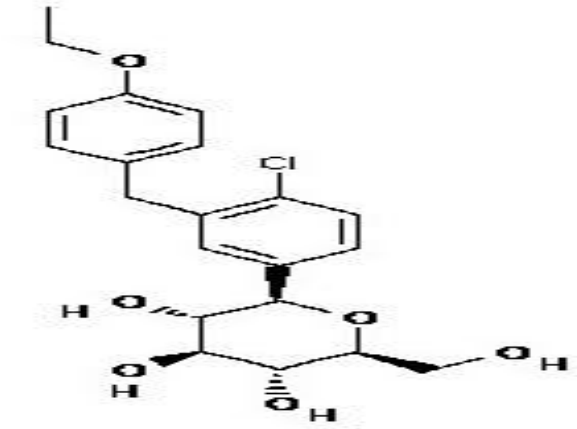
Dapagliflozin, a recently authorized medication for the treatment of people with T2DM, is an effective SGLT2 inhibitor. These inhibitors have benefits beyond glycemic control, including as modest heart rate and regular weight loss, increased insulin levels, and enhanced beta-cell efficiency. Its highly specific SGLT2i inhibits the SGLT2 receptors found in the S1 region of the proximal kidney tubules, reducing renal glucose absorption. It is available as tablet for oral use[29].

IUPAC NAME: -

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-6- (hydroxymethyl) oxane-3,4,5-triol.

BRAND NAME: - FORXIGA

Structure:-



Molecular Formula: - $C_{21}H_{25}ClO_6$

Molecular weight: - 408.9g/mol

Mechanism of action: -

Dapagliflozin, a selective and reversible SGLT2 inhibitor, reduces blood sugar levels without the need of insulin by massively reducing glucose absorption. In T2DM patients, dapagliflozin increases glycogen synthesis and also improving insulin levels**.**

Pharmacokinetics: -

In the hepatocyte, the enzyme glucuronic acid converts the drug dapagliflozin to its inactive metabolite, dapagliflozin 3-O-glucuronide. Dapagliflozin does have an overall plasma terminal half-life of 13 hours (10 mg dosing). Because renal dysfunction inhibits excretion, dapagliflozin and its metabolites are mainly cleared through the urine.[30]

Pharmacodynamics: -

Although sodium excretion through the kidneys temporarily increases, serum sodium could not seem to change. Renal uric acid excretion rises momentarily, while serum levels continuously drop. Even though the actual cause of the reduced plasma creatinine levels is unknown, it has recently been suggested that it may be caused by either reduced uric acid absorption at the capillary beds of the renal tubule or hyperglycemia-induced GLUT9 type 2 in the proximal tubule[31].

Side Effects: -

- Genital fungal infection,
- Increased thirst
- Nausea
- Urinary tract infection
- fungal infection of vagina[32]

Dosage & Administration: -

Dapagliflozins beginning dose is five milligrams taken once day, before the first breakfast.[30]

Table 2: Analytical Methods for Determination of Dapagliflozin: -

Technique	Extensive Method Condition	Detection Outline	Formulation	Reference
RP-HPLC	**Mobile Phase: -** Ortho Phosphoric Acid: Acetonitrile (45:55 v/v) **Stationary Phase: -** BDS column (250×4.5mm, 5µ) **Flow Rate**: 1ml/min **Linearity Range**: 25-150µg/ml **Retention Time**: 2.963 min **Correlation Coefficient(r2)**: 0.999 **LOD**: 0.6 µg/mL **LOQ:** 1.8µg/mL **% Recovery: -** 99.8% **Solvent: -** Methanol	245nm	API	(33)

UV SPECTROSCOPY	**Solvent**: Water **Linearity Range:** 0.5-0.9µg/mL **Correlation Coefficient(r2**): - 0.994	237nm	API	(34)
RP-HPLC	**Stationary phase: -** Column c18 **Mobile phase: -** Acetonitrile: di potassium hydrogen phosphate (PH-6.5) (40:60) **Flow rate: -** 1mL/min **Stationary Phase:** Column C18	225nm -	Human plasma	(35)
LC-MS	**Mobile Phase: -** Water/acetonitrile (60:40)	-	Human Plasma	(36)
LC MS/MS	**Stationary Phase: -** C18 (2.1×100 mm, 2.7 µm) column **Mobile phase:** Ammonium acetate: Acetonitrile (20:80, v/v) **Flow rate**: - 0.2 mL/ min **concentration range**: **Dapagliflozin**: -25-500 ng/mL and **metformin**: - 100-2000 ng/mL **LOD**: - 6.83 ng/mL & 20.70 ng/mL **LOQ: -** **Dapagliflozin: -**29.45 ng/mL **Metformin:** 89.24 ng/mL	-	Dosage form	(37)
UV Spectroscopy	**Solvent: -** Methanol **Correlation Coefficient (r2): -** metformin: - 0.993 Dapagliflozin: -0.991 **% RSD**: **Metformin**: -1.102% **Dapagliflozin**-1.353%	225nm&237nm	Synthetic mixture	(38)
Fluroscence Spectroscopy	**Concentration range: -** 100–1000 ng mL^{-1} **LOD: -** 26.49 ng mL^{-1} **LOQ: -**79.48 ng mL^{-1}**%** **Recovery: -** 100.43 ± 1.15.	278nm	Tablets	(39)
LC	**Stationary phase:** (Lichrosorb 100-5- NH2) column **Mobile phase: -** NaH2PO4 buffer (10 mM, pH 2.8): acetonitrile (18.5:81.5, v/v) **Concentartion ranges: -** 3.75–30 µg/ml **Flow rate: -** 2 mL/min^{-1} **LOD**: - 0.135, µg/mL **LOQ**: -0.233, µg/mL	-	-	(40)
RP-HPLC	**Stationary phase: -** C18 column (250×4.6mm; 5µm) **Mobile phase: - A**cetonitrile: Water (40:60%v/v) **Concentration range**: - 1-16 µg/ml **% Recovery: -** 98-102% **LOD: -** 0.049µg/ml **LOQ**: -0.1485 µg/ml	277nm	Dosage Form	(41)

RP-HPLC (Dapagliflozin and Saxagliptin)	**Stationary phase: -** Cosmosil C18 (250×4.6ID) column **Mobile Phase: -** Methanol:Potassium phosphate buffer (80:20v/v) **Flow rate** 0.8mL/min **% Recovery: Dapagliflozin**: - 99.51 -99.82% **Saxagliptin**: -99.26-99.48% **LOD: -** dapagliflozin**: -** 0.04262µg/mL& **Saxagliptin: -** 0.004065µg/mL **LOQ: - dapagliflozin**: - 0.0371µg/mL **Saxagliptin: -**0.0246µg/mL	-	Tablets	(42)

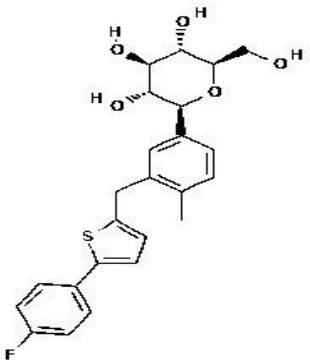
CANAGLIFLOZIN

Canagliflozin is a novel oral antidiabetic agent belonging to the class of sodium–glucose cotransporter 2 (SGLT2) inhibitors. it inhibits glucose reabsorption in the proximal tubule, leading to increased urinary glucose excretion and subsequently to reduction in plasma glucose concentration, in individuals with hyperglycemia.[43] The first SGLT2 inhibitor to be legalized in the US was canagliflozin in March 2013.[44] it is white to off white solid with a melting point of 95-105°C. It is soluble in many organic solvents (methanol, Dimethyl sulfoxide) and insoluble in aqueous media.[45]

IUPAC NAME: -

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-[3-[[5-(4-fluorophenyl) thiophen-2-yl] methyl]-4-methylphenyl]-6(hydroxymethyl) oxane-3,4,5-triol.

BRAND NAME: - INVOKANA



Structure: -

Molecular weight: - 444.5g/mol
Molecular formula: - $C_{24}H_{25}FO_5S$

Mechanism of action: -

Canagliflozin is a drug of the gliflozin family that inhibits the body's sodium glucose cotransporter 2 (SGLT2). The primary function of SGLT2 is to prevent the glucose reabsorption in the primary tubule of the kidney. Drugs in the gliflozin class are more effective for treating T2DM. Increased urine glucose excretion and reduced glucose reabsorption are both brought on by canagliflozin. Because the strength of these medicines depends on how much glucose is passed through the glomeruli into the tubular lumen.[46]

Pharmacokinetics: -

When taken orally, it takes 1 to 2 hours for the serum levels to reach its peak.Canagliflozin does have a bioavailability of around 65% if taken orally. It binds mostly to albumin with a high plasma protein binding level (99%). Food has few impacts on how much it absorbs. Its primary mechanism of metabolism is glucuronidation, and its half-life is 11 hours for a dose of 100 mg and 13 hours for a 300-milligram dose.[41]

Pharmacodynamics: -

Canagliflozin, an SGLT2 inhibitor, gives hypoglycemic benefits. The most 90% of the glomerular filtration of filtered glucose in the kidneys is carried out by the protein SGLT2, that is presented in the proximal renal tubules, a specific inhibitor of SGLT2, canagliflozin lowers blood glucose levels via increasing urine glucose excretion, decreasing renal glucose reabsorption, and decreasing the kidney tolerance for glucose (RTG).[47]

Side Effects: -

- Hyperkalemia
- Urinary tract infections
- common fungal vaginal infections in both females and uncircumcised males.
- hypotension
- increased thirst, and hypotension
- polyurea
- Hyperlipidemia.[48]

Dosage & Administration: -

The recommended starting dose for canagliflozin is hundred milligrams just once, given just before breakfast. Patients who take Canagliflozin 100 mg once day and need more glycemic control can have their dose extended to 300 mg once daily when they have an eGFR of 30 ml / min square metres or higher.[49]

Table 3: Analytical Methods for Determination of Canagliflozin

Technique	Extensive Method Condition	Detection Outline	Formulation	Reference
RP-HPLC	**StationaryPhase:** (Hypersil BDS, C18 100 x 4.6 mm, 5µ) **Mobile Phase: -** (0.1% ortho phosphoric buffer: acetonitrile (53:47), water and acetonitrile (50:50) **LOD: -** 0.23µg/ml **LOQ: -** 0.7µg/ml, **Flow Rate:** s 1.1ml/min **% Recovery:** -99.83%.	240 nm	Pharmaceutical Dosage form	(50)
UHPLC–MS/MS	**Stationary Phase:** BEH C18 column (100×2.1mm, i.d. 1.7µm) **Mobile Phase:** Acetonitrile:water (80:20, v/v) **Flow Rate:** 0.3mL/min	283 nm	Rat Plasma	(51)
LC-MS	**Stationary phase: -** Zobrax xdb phenyl (75x4.6mm,3.5mm) **Mobile phase: -** methanol: acetate buffer (80:20 v/v)	-	Human plasma	(52)
HPLC	**Stationary phase: -**Kromosil C18 (100 mm x 4.6 mm 5 µm) column kept **Mobile Phase: -** Acetonitrile:water PH 2.5 adjusted with orthophosphoric acid, 50: 50v/v **Flowrate:** 1.0mL/min. **Concentration range**: -10 to 200 µg/ml.	260 nm	API	(53)
HPTLC	**Stationary Phase: -** Silica Gel 60F254 **Mobile Phase**: - Toluene: Ethyl acetate: Methanol (2:2:1, v/v/v) **Linearity: -** 10- 500 ng mL^{-1} **LOD**: 0.39 µg/ml **LOQ:** 1.19 µg/ml **% Recovery: -** 99.8 %	290 nm	Tablets	(54)
UV-Spectroscopy	**Solvent: -** Phosphate buffer **concentration range**: -1-6 $mcgml^{-1}$. **Mean recovery: -** 80-120%	289 nm	Tablets	(55)
LC-MS/MS	**Stationary phase:-**COSMOSIL 5CN-MS(150×4.6mm, 5µm) column. **Mobile phase: -**methanol Mammonium formate in water, pH5 (75:25,v/v) **Concentration range**-2.50–2500ng/mL	-	Human plasma	(56)
LC-MS/MS	**Stationary phase:-**Inertsil ODS5µm C18,50×4.60mm **Mobile phase:-**30:70v/v of 0.01M ammonium acetate: methanol **Flowrate:-**0.8ml/min **% Recovery**:-102.05%	-	Rabbit plasma	(57)
HPTLC	**Stationary phase:-**Glass coated silicagel 60F254 **Mobile phase:-**binary mixture of chloroform: methanol 9:1(%,v/v) **Linearity range:-**200–3200ng/ml.	289 nm	Human plasma	(58)

RP-HPLC (Metformin & canagliflozin)	**Stationary phase:-**Kromosil C18 250 column, **Mobile phase:-**mixture of phosphate buffer andacetonitrile in the ratio of65:35%v/v **LOD**:-**metformin**0.30µg/ml **Canagliflozin-**0.361µg/ml**LOQ:-** **Metformin-**0.91µg/ml **canagliflozin-**1.094µg/ml **Flowrate:-**1.0ml/min	290nm	Tablets	(59)

CONCLUSION

Sodium glucose cotransporter 2(SGLT2) used for the treatment of T2DM. Various analytical methods tabulated for Empagliflozin, Dapagliflozin, Canagliflozin were obtained from the literature survey of reference book and research articles. The developed methods help in understanding and determining the toxicity of these compounds. The routine analysis also assists the quality of formulation and gives the idea about further improvement of technique. This survey involves study of pharmacokinetics, pharmacodynamics, dosage administration, side effects of drugs and analytical techniques such as HPLC, UPLC, HPTLC, GC-MS, LCMS, UV-spectroscopy on selected SGLT2 inhibit

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