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DAPAGLIFLOZIN: AN ANTI-DIABETIC DRUG WITH CARDIOVASCULAR BENEFITS

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ABSTRACT: Type 2 diabetes mellitus (T2DM) is a chronic disease, and most patients ultimately require two or more anti-hyperglycemic drugs along with lifestyle changes to achieve and maintain glycaemic control. Sodium-glucose co-transporter 2(SGLT2) inhibitors, such as Dapagliflozin, are the newest class of antidiabetic drugs approved for the treatment of T2DM. Dapagliflozin is a highly selective SGLT2 inhibitor that decreases glucose reabsorption by kidneys and thus lowers blood glucose by increasing glucose excretion in urine output. Dapagliflozin effectively improves glycaemic control by increasing the renal excretion of excess glucose. In clinical trials, dapagliflozin has been well-tolerated and safe to be administered to the major population. It has additional benefits of weight loss, low risk of hypoglycemia, reduction in blood pressure, and cardiovascular benefits. Dapagliflozin can be administered as monotherapy on in combination with other antidiabetic drugs. Thus, Dapagliflozin offers a novel treatment option for type 2 diabetes mellitus with additional benefits.

INTRODUCTION: [1, 2] Type 2 diabetes affects millions of people worldwide, and India is suspected of being the world's diabetes capital with 72.94 million cases in 2017. Metformin is considered a first-line treatment for type 2 diabetes, followed by sulfonylureas. Despite a large number of drugs already being available for the management of hyperglycemia in T2DM, these glucose-lowering agents are not adequately effective in maintaining long-term glycaemic control in the majority of patients. Furthermore, most anti-hyperglycemic agents are associated with adverse events such as hypoglycemia and/or weight gain, which exert counterproductive effects and hamper adherence to treatment. Thus, there remains a medical need for improving pharmacological therapy of T2DM.

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Inhibitors of sodium-glucose co-transporter type 2 (SGLT2) are new glucose-lowering agents with an insulin-independent mode of action. They specifically target the kidney by blocking the reabsorption of filtered glucose, thus leading to increased urinary glucose excretion, especially when hyperglycemia is present. This mechanism of action holds promise for patients with T2DM not only in terms of improvements in glycaemic control along with a limited risk of hypoglycemia but also has potential benefits of weight loss due to increased glucosuria and reduction in arterial blood pressure associated with the osmotic effect. SGLT2 inhibitors may be used as monotherapy or in combination with any other glucose-lowering agent.

The pharmacokinetic characteristics of SGLT2 inhibitors show an excellent oral bioavailability and long elimination half-life allowing once-daily administration. Furthermore, these agents share a negligible risk of drug-drug interactions.

SGLT2 Inhibitors Development: SGLT2 inhibitors or gliflozins development was initiated from Phlorizin, a naturally occurring glucoside

which was known to produce renal glycosuria along with blocking intestinal glucose reabsorption. Phlorizin, when isolated, showed potency but was a non-selective inhibitor of SGLT1 and SGLT2 proteins. Due to the poor oral bioavailability, it was not used in humans, but it played an important role in the development of other SGLT2 inhibitors [3].

Most of the SGLT2 inhibitors are glucoside analogs, whether it be o-glucosides or c-glucosides, c-glucosides differ in pharmacokinetic parameters from o-glycosides. Dapagliflozin (AstraZeneca) was the first c-glucoside drug and first highly selective SGLT2 inhibitor approved by European Medicines Agency (EMA) in Europe (as Forxiga) in 2012 and later on in the United States (as Farxiga) in 2014.

The first SGLT2 inhibitor to be marketed in the US as canagliflozin (Invokana, Janssen), launched in 2013 and later that year the American Association of Clinical Endocrinologists (AACE) algorithm was updated to include SGLT2 inhibitors, stating they could provide a therapeutic alternative in patients with T2DM in whom metformin is not tolerated or otherwise contraindicated.

Other SGLT2 inhibitors are empagliflozin (Jardiance, Boehringer Ingelheim, and Eli Lilly and Company), approved in Europe in 2014, ipragliflozin (Suglat, Astellas), approved in Japan in 2014. Also, a number of other SGLT2 inhibitors are in various stages of clinical development. **Table 1** enlists the various SGLT2 inhibitors.

TABLE 1: LIST OF VARIOUS SGLT2 INHIBITORS [3]

Generic name	Brand name	Doses available (mg)	Proposed indication	Approval status
Canagliflozin	Invokana	100 and 300	qam	Approved in 2013 (US)
Dapagliflozin	Farxiga/Forxiga	5 and 10	qam	Approved in 2014 (US)
Empagliflozin	Jardiance	10 and 25	qam	Approved in 2014 (US)
Ipragliflozin	Suglat	25 and 50	qam	Approved in 2014 (Japan)
Luseogliflozin	Lusefi	2.5 and 5	qam	Approved in 2014 (Japan)
Tofogliflozin	Apleway/Deberza	20	qam	Approved in 2014 (Japan)
Ertugliflozin	Steglatro	5 and 15	qam	Approved in 2017 (US)
Remogliflozin	NA	NA	NA	Not approved
Sergliflozin	NA	NA	NA	Not approved
Sotagliflozin	Zynquista	200 and 400	qam	Approved in 2019 (EU)

Drug Profile, Structure and Synthesis of Dapagliflozin: [4]

Category: Oral Hypoglycaemics

Molecular formula: $C_{21}H_{25}CLO_6$

Molecular Weight: Average - 408.873; Mono-isotopic - 408.134.

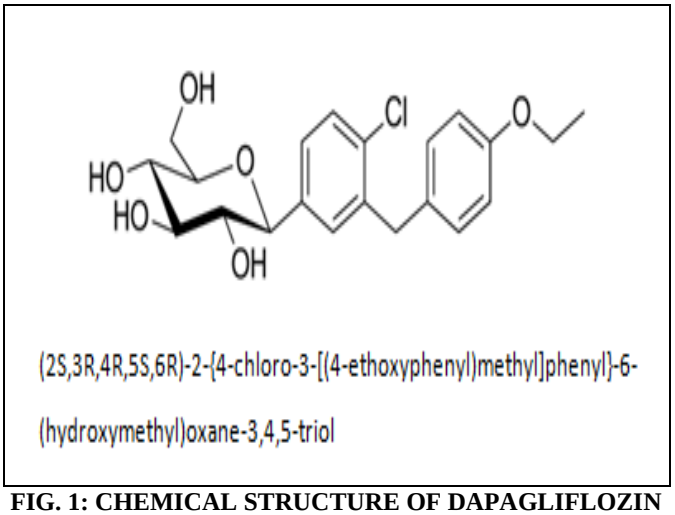

FIG. 1: CHEMICAL STRUCTURE OF DAPAGLIFLOZIN

Physicochemical Properties:

- **Description:** White to off-white powder
- **Solubility:** Soluble in ethanol, slightly soluble in water and freely soluble in DMSO
- **Melting point:** 65-70°C
- **logP:** 2.11
- **pKa (Strongest Acidic):** 12.57
- **pKa (Strongest Basic):** -3

Dapagliflozin as an SGLT2 Inhibitor: Dapagliflozin was approved for maintaining the blood glucose levels in patients having type 2 diabetes, apart from being hypoglycaemic it has additional benefits of reducing body weight and blood pressure which is useful in patients suffering from obesity and hypertension along with diabetes [5, 12]. Ongoing clinical trials regarding the cardiovascular benefits of Dapagliflozin are depicted in **Table 2**. Dapagliflozin is a relatively new entrant in anti-diabetic therapy, and there are a number of trials going on worldwide regarding its additional benefits and safety.

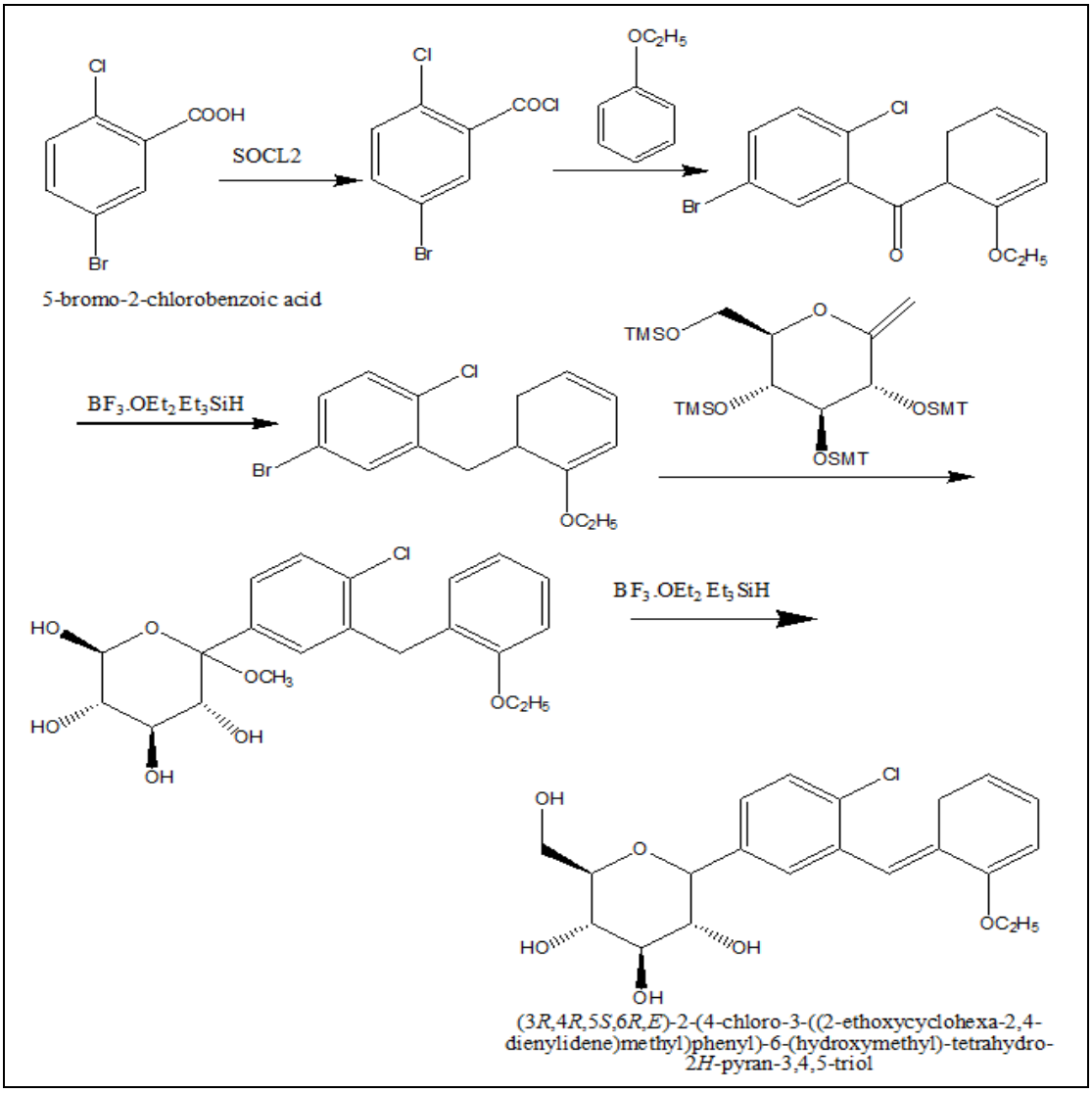

FIG. 2: CHEMICAL SYNTHESIS OF DAPAGLIFLOZIN

TABLE 2: ONGOING RECENT CLINICAL TRIALS CONCERNING CARDIOVASCULAR BENEFITS OF DAPAGLIFLOZIN [15-20]

Study title	Conditions	Interventions	No. of patients enrolled	Study start year	Projected year of completion
Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure [15]	Heart failure with a preserved ejection fraction	Dapagliflozin	4700	2018	2021
Effect of Dapagliflozin on night-time blood pressure [16]	Type 2 diabetes	Dapagliflozin 10 mg and placebo tablet	225	2019	2020
Dapagliflozin and measures of cardiovascular autonomic function in patients with type 2 diabetes [17]	Type 2 diabetes and cardiovascular diseases	Dapagliflozin and Glimepiride	45	2017	2020
Dapagliflozin in preserved ejection fraction heart failure [18]	Chronic heart failure with preserved systolic function	Dapagliflozin 10 mg	320	2017	2019
Dapagliflozin effect on symptoms and biomarkers in patients with heart failure [19]	Chronic heart failure with reduced systolic function	Dapagliflozin	263	2016	2019
Study to access the effect of Dapagliflozin on the reduction of central blood pressure [20]	Type 2 diabetes	Dapagliflozin 10 mg and Glimepiride 4mg	159	2016	2019

Dapagliflozin Pharmacodynamics: [8] SGLTs, a family of membrane proteins responsible for the transport of glucose, amino acids, and other substances in the proximal renal tubule and the intestinal epithelium in kidneys. Almost all of the glucose filtered daily in the glomeruli of healthy adult kidneys is reabsorbed via a complicated process involving various transport mechanisms. The SGLT2 protein co-transports sodium and glucose across the brush border membrane of the proximal renal tubule into the tubular epithelial cells; a process is driven by the sodium gradient between the tubule and the cell, thereby it facilitates secondary active transport of glucose. Glucose is then passively reabsorbed from the epithelial cells into the interstitium by a glucose transporter protein. The main role of SGLT1 is glucose absorption in the gastrointestinal tract, but it also accounts for approximately 10% of glucose reabsorption in the proximal tubule. SGLT2 is a crucial protein that is majorly responsible for 90% of the kidney's glucose reabsorption.

Dapagliflozin is a competitive and highly selective inhibitor of SGLT2, resulting in decreased renal reabsorption of glucose and increased urinary glucose excretion, thereby reducing blood glucose levels by a mechanism that is independent of the action of insulin and sensitivity of the cells to uptake insulin. Therefore, dapagliflozin is also suitable for patients who have decreased functional pancreatic cells or suffering from pancreatic insufficiency.

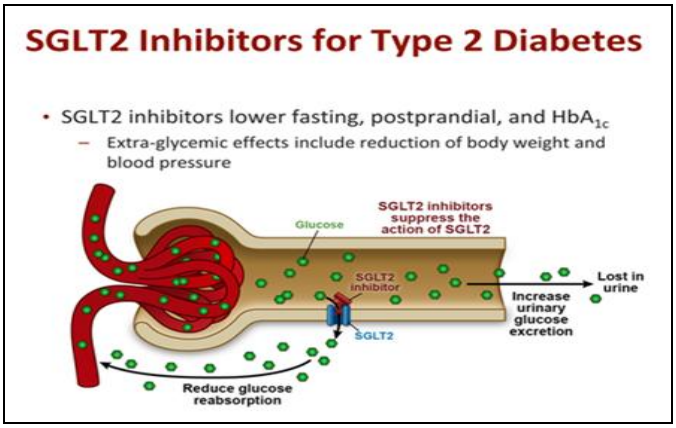

FIG. 3: MECHANISM OF ACTION OF DAPAGLIFLOZIN

Dapagliflozin Pharmacokinetics: [9-11]

Absorption: Following oral administration, the maximum plasma concentration (C_{max}) of dapagliflozin is usually attained within 2 h under a fasting state. The oral bioavailability of 10 mg dose of dapagliflozin is 78%. Dapagliflozin is administered as once daily in the morning (qam).

Distribution: Dapagliflozin is a highly protein-bound drug; protein binding of dapagliflozin is approximately 91% and is not altered in patients with renal or hepatic impairment.

Metabolism: Metabolism of dapagliflozin is majorly by UGT1A9 and minorly by CYP. A primary metabolite is 3-O-glucouronide, which is an inactive metabolite.

Elimination: Dapagliflozin and its metabolites are primarily eliminated by the kidney. 75% of the drug is excreted in urine and 21% in faeces as parent drug and metabolites. In urine, less than 2% of the dose is excreted as parent drug, and in faeces approximately 15% of the dose is excreted as parent drug. **Table 3** compares the pharmacokinetics of dapagliflozin with other SGLT2 inhibitors.

TABLE 3: PHARMACOKINETICS OF VARIOUS SGLT2 INHIBITORS [9, 10]

Drug	Bioavail-ability (%)	Protein binding (%)	t_{max} (h)	$t_{1/2}$ (h)
Canagliflozin	65	99	1-2	10.6
Dapagliflozin	78	91	1-1.5	12.9
Empagliflozin	75	86.2	1.5	13.2
Ipragliflozin	90	96.3	1	15-16
Tofogliflozin	97.5	82.3-82.6	1	5.4
Ertugliflozin	70-90	93.6	0.5-1.5	11-17

Drug Interactions: Co-administration of dapagliflozin with metformin, glimepiride, pioglitazone, or sitagliptin had no effect on the maximum plasma concentration of dapagliflozin or the area under the plasma concentration-time curve. In addition, dapagliflozin did not affect the pharmacokinetics of co-administered drugs. Similarly, no meaningful drug-drug interactions were noted between dapagliflozin and simvastatin, valsartan, warfarin, or digoxin, and therefore, no dose adjustments are recommended for dapagliflozin.

Dapagliflozin as Monotherapy: Dapagliflozin was evaluated at doses ranging from 1 to 50 mg once daily when added to background diet and exercise and compared with metformin monotherapy or administered as monotherapy in patients. Dapagliflozin as monotherapy improved

glycaemic index control and also reduced body weight without causing hypoglycemia. Significant reductions in fasting plasma glucose (FPG) and body weight for dapagliflozin versus placebo or metformin were observed. Hypoglycemia was uncommon in dapagliflozin-treated patients but genital and urinary tract infections were more common in dapagliflozin groups than in controls [13, 14].

Add-on Combination Therapy with Metformin: After conducting the 24-week placebo-controlled study on 546 patients with T2DM having inadequate glycaemic control (HbA1c ≥7% and ≤10%), statistically significant improvements in HbA1c and FPG were observed along with a reduction in body weight compared with either of the monotherapy treatments [21]. Considerable changes in systolic blood pressure relative to placebo plus metformin with dapagliflozin plus metformin were also there.

Add-on Combination Therapy with Insulin: A total of 808 patients having T2DM with inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) were involved for a 24-week study to evaluate Dapagliflozin as an add-on to insulin. The study included 50% of the patients on insulin monotherapy and 50% on one or two other anti-diabetic drugs along with insulin [21]. Dapagliflozin provided improvement in HbA1c and reduction in body weight compared with placebo resulting in a reduction of mean insulin dose.

Add-on Combination Therapy with a Sulfonylurea: Trials were conducted on 597 patients having T2DM with inadequate glycaemic control (HbA1c ≥7% and ≤10%) in 24-week study and glimepiride along with dapagliflozin was evaluated [21]. In combination, significant improvement in HbA1c, FPG, and 2-h elevated postprandial glucose (PPG) were observed.

Add-on Combination Therapy with a Thiazolidinedione: A total of 420 patients having T2DM with inadequate glycaemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week study [21]. Pioglitazone was utilized as thiazolidinedione in combination with dapagliflozin, improvements in HbA1c, FPG and 2-h PPG along with the significant reduction in body weight was observed.

Add-on Combination Therapy with a Dipeptidyl peptidase-4 (DPP) Inhibitor: Placebo-controlled study involving 452 patients with T2DM having inadequate glycaemic control (HbA1c ≥7% and ≤10%) was conducted for 24 weeks [21]. Dapagliflozin in combination with sitagliptin provided significant improvements in HbA1c, FPG and reduction in body weight compared with placebo plus sitagliptin.

Safety and Tolerability of Dapagliflozin: [6, 7] The safety of dapagliflozin as monotherapy and as add-on therapy to existing antidiabetic treatment in patients with T2DM has been evaluated in multiple randomized controlled trials, majority of adverse effects were of mild to moderate intensity. The tolerability profile demonstrated in the short-term studies was maintained consistently in patients receiving long-term dapagliflozin treatment. No substantial adverse effects on serum electrolytes, liver function, or renal function were reported.

Volume-related events, *i.e.,* hypotension, dehydration, and hypovolemia, were infrequent, and none were serious. Numerically higher rates of dyslipidemia with dapagliflozin versus placebo have been reported. There are some reports about patients on SGLT2 inhibitor treatment developing diabetic ketoacidosis.

Adverse Drug Reactions Associated with Dapagliflozin: [22-25] Patients which are undergoing dapagliflozin therapy should be informed of its adverse drug reactions and precautions should be taken. The drug is associated with following adverse drug reactions, out of which most common are genital mycotic infections and urinary tract infections.

Genital Mycotic Infections: Risk of genital mycotic infections are increased in patients, particularly in those with prior genital mycotic infections.

Urinary Tract Infections: Dapagliflozin and other SGLT2 inhibitors increase the risk of urinary tract infections (UTI), and serious UTIs are reported with dapagliflozin.

Ketoacidosis: Patients having symptoms of ketoacidosis, regardless of blood glucose level, should discontinue dapagliflozin as fatal cases of

ketoacidosis are reported for this drug. Risk factors for ketoacidosis should always be considered before initiating dapagliflozin therapy.

Kidney Injury and Renal Impairment: Kidney damage can occur due to dehydration, Dapagliflozin increases serum creatinine level and decreases estimated glomerular filtration rate (eGFR) thus it is not suitable for patients with impaired renal function and patients on dialysis. Patients with an eGFR constantly between 30 and <60 mL/min/1.73 m^2 are not recommended dapagliflozin.

Hypotension: Symptomatic hypotension occurs with dapagliflozin due to intravascular volume contraction. Elderly patients, patients with impaired renal function, and those on loop diuretics should assess correct volume status before initiating the drug.

Bladder Cancer: Dapagliflozin should not be used in patients with active bladder cancer or with a history of bladder cancer as an imbalance in bladder cancers was observed in clinical trials. Although there is insufficient data regarding the drug's effect on pre-existing bladder tumors, but caution has to be taken.

Fournier's Gangrene: This is a life-threatening disease that has been reported in patients receiving SGLT2 inhibitors, including dapagliflozin. Patients having pain or tenderness, swelling in the genital or perineal area along with fever, should be assessed and discontinue the drug. This adverse drug reaction is rare, but cases reported had serious outcomes, including death.

Hypoglycemia: Hypoglycaemia is usually not associated with dapagliflozin but may occur if it is coadministered with insulin or other anti-diabetic drugs.

Dapagliflozin for Special Population: [21]

Renal Impairment: Dapagliflozin acts by inhibiting SGLT2 proteins present in the kidney therefore, adequate functioning of the kidney is required for the efficacy of the drug. Patients having mild to moderate renal impairment had acceptable effects with higher systemic exposure of dapagliflozin, but dapagliflozin is contraindicated for patients with severe renal impairment, end-stage renal disease, and patients on dialysis.

Hepatic Impairment: Patients with mild, moderate, or even severe hepatic impairment need no dose adjustment. But in the case of patients with severe hepatic impairment, the benefit to risk ratio should be individually assessed due to the unavailability of enough safety and efficacy data in this population.

Pregnancy: Dapagliflozin is not recommended during second and third trimesters of pregnancy. The estimated risk of major birth defects is 6-10% in women having pre-gestational diabetes with a HbA1c greater than 7% and 20-25% in women with HbA1c greater than 10%. The estimated risk of major birth defects and miscarriage in pregnancies is 2-4% and 15-20%, respectively.

Lactation: Dapagliflozin is not recommended during breastfeeding since human kidney maturation occurs during the first two years of life, there is a risk of under developing kidney of the infant

Pediatric and Geriatric Use: Safety and efficacy data have not been established for the pediatric population. For the geriatric population, no dose adjustment is required based on age, but renal impairment was observed as an adverse reaction in this population.

TABLE 4: ANALYTICAL METHODS FOR DAPAGLIFLOZIN [26-32]

Analytical technique	Description		Authors	References
	Sample	Specification		
RP-HPLC	Tablet	RP-HPLC UV	Debata J *et al*	26
	API	RP-HPLC UV	Mante GV *et al*	27
HPLC	Tablet	Stability indicating HPLC	Verma MV *et al*	28
UV	Tablet	First and second order derivative method	Mante GV *et al*	29
	API and Tablet	NA	Chitra KP *et al*	30
LC-MS/MS	Rat plasma	Negative ionization mode	Aubry AF *et al*	31
	Human plasma	Negative ionization mode	Ji QC *et al*	32

Analytical Methods Available for the Estimation of Dapagliflozin: A few analytical methods are available for the estimation of dapagliflozin, comprising of HPLC methods, UV-spectrophoto-

metric methods, and LC-MS/MS methods. **Table 4** enlists the analytical methods available for the estimation of dapagliflozin.

CONCLUSION: Diabetes is still a worldwide challenge in spite of various anti-diabetic drugs available in the market. Continuous research is in progress to discover newer drugs that can provide better glycaemic control. SGLT2 inhibitors like Dapagliflozin are effective in maintaining better glycaemic control in patients on other anti-diabetics but with uncontrolled blood glucose levels. With its additional benefits like reduction in body weight and hypotension, it is favored over other available anti-diabetics. Dapagliflozin has shown improvement in cardiovascular function as well and is beneficial to patients suffering from cardiovascular disease, but more study and conclusive data are required before it is recommended for this indication.

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