WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Dapagliflozin: A Game-Changer in Diabetes Management and Beyond

Mishri Patel[1], Nishi Patel[2], Diya Parmar[3], Dr. Vaibhavkumar Patel[4]

[1,2,3]Student (Doctor of Pharmacy), Saraswati Institute of Pharmaceutical Sciences, Gandhinagar

[4]Guide, Saraswati Institute Pharmaceutical Sciences, Gandhinagar

ABSTRACT

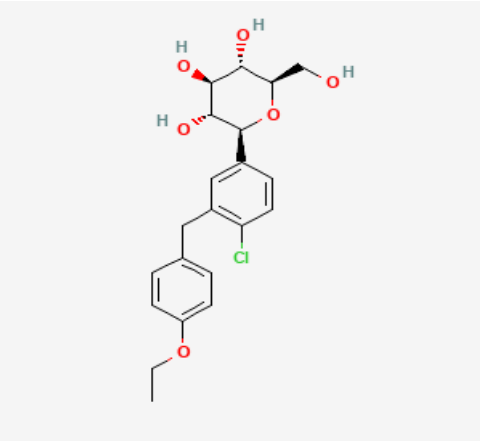
Dapagliflozin is an innovative pharmaceutical compound that has garnered significant attention in the field of diabetes management. This abstract aims to provide a concise overview of dapagliflozin, its mechanism of action, clinical applications, potential benefits and other parameters[1 2.] Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that works by blocking the reabsorption of glucose in the kidneys, following increased urinary glucose excretion. By targeting this specific mechanism, dapagliflozin helps lower blood glucose levels in patients with type 2 diabetes mellitus. Several clinical trials have demonstrated the efficacy and safety of dapagliflozin in improving glycemic control. The drug has been shown to decrease fasting plasma glucose, postprandial glucose excursion and HbA1c levels. Additionally, dapagliflozin has been associated with weight loss and a modest decrease in blood pressure. Furthermore, dapagliflozin has shown potential benefits beyond glycemic control. It has been linked to a reduction in cardiovascular events and hospitalizations for heart failure, making it an attractive therapeutic option for patients with diabetes and a high cardiovascular risk. The adverse effects of dapagliflozin are generally mild, with the most common being genital mycotic infections and urinary tract infections. However, the benefits of dapagliflozin in improving glycemic control and reducing cardiovascular risks have outweighed the risks in clinical trials. In conclusion, dapagliflozin, as an SGLT2 inhibitor, represents a promising addition to the armamentarium of diabetes management. Its ability to lower blood glucose levels, promote weight loss, and reduce cardiovascular events makes it an attractive choice for patients with type 2 diabetes and a high cardiovascular risk profile. Further research and real-world evidence will continue to refine our understanding of dapagliflozin's full potential in the management of diabetes and its associated complications [3 4].

Key words – dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, diabetes management, cardiovascular benefits.

HISTORY

The development of dapagliflozin can be traced back to the late 1990s and early 2000s. Bristol-Myers Squibb, a pharmaceutical company, initiated as a potential treatment for diabetes. In collaboration with AstraZeneca, BMS discovered dapagliflozin and conducted preclinical and clinical studies to assess its efficacy and safety. Clinical trials were conducted to analyze the effectiveness of dapagliflozin in improving glycemic control and other metabolic parameters including reduced blood glucose levels, body weight and blood pressure in patient with type 2 diabetes. Based on the positive results from clinical trials, BMS and AstraZeneca submitted a new Drug Application for dapagliflozin to the US. Food and Drug Administration in 2011. However, the FDA requested additional data on dapagliflozin safety and cardiovascular effects before approving the medication. The DECLARE-TIMI 58 trial analyzed the cardiovascular safety profile of dapagliflozin in large population of patient and even demonstrated cardiovascular benefits. In January 2014, dapagliflozin received FDA approval under the brand name Farxiga for the treatment of type 2 diabetes. Since then, approved by regulatory authorities in various countries worldwide counting the European Medicines Agency and other healthcare industries. Also have demonstrated in reducing the risk of heart failure hospitalization and improving renal outcomes in patient with type 2 diabetes [5 6].

Physicochemical properties



(Fig.1)

Dapagliflozin is an oral medication that is commonly prescribed to treat individuals with type 2 diabetes. Its primary function is to help reduce high blood sugar levels. Dapagliflozin belongs to a group of drugs known as Sodium-glucose co-transporter 2 (SGLT2) inhibitors. Previously, dapagliflozin was available in tablet form for oral consumption and was marketed under the brand name Farxiga (Forxiga in some countries). However, researchers have also explored alternative formulations of dapagliflozin, such as dapagliflozin-loaded solid lipid nanoparticles (SLNs). The development of these SLNs involved a process that combined high shear homogenization and ultra-sonication methods. By experimenting with different concentrations of surfactants, and sonication time, the researchers were able to achieve enhanced solubility of the drug in the molten lipid state. The formulation process for dapagliflozin-loaded SLNs was relatively straightforward and reproducible. In total, seventeen batches of SLNs were created using a design called Box-Behnken Design (BBD). This design involved three independent variables: lipid content, surfactant concentration, and sonication time. The outcomes of this experimentation were evaluated based on measures such as percentage encapsulation efficiency (%EE), cumulative drug release (% CDR), and particle size [5 6].

Pharmacokinetics

Dapagliflozin does not have a specific BCS (Biopharmaceutics Classification System) classification as it is not listed in the BCS guidance documents or literature. The BCS is a classification system used to predict the oral absorption of drugs based on their solubility and permeability characteristics. It classifies drugs into four categories: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability).

However, based on its physicochemical properties and available information, dapagliflozin can be considered to have relatively high solubility and high permeability. It is known to have good aqueous solubility and its absorption is not limited by permeability barriers. Therefore, dapagliflozin can be considered to have characteristics consistent with BCS Class I or Class II drugs, which generally have good oral absorption. Absorption- When dapagliflozin is taken orally, quickly reaches its highest concentration in the bloodstream within one hour if the patient has not eaten anything before taking the medication. However, if the patient has consumed a high fat meal, the time taken for dapagliflozin to reach its maximum concentration increases to two hours. Additionally, when dapagliflozin is taken after a high fat meal, the maximum concentration in the blood is reduced by half compared to when taken on an empty stomach. Despite this change in concentration there is no need to adjust the dosage of dapagliflozin it is also important to note that oral dapagliflozin has a bioavaibility of 78% which means that approximately 78% of medication is absorbed into bloodstream when taken by mouth. Metabolism- Dapagliflozin undergoes a process called glucuronidation, where it is primarily converted into an inactive metabolite called 3-O-glucuronide (accounting from approximately 60.7% of the metabolism process). Aside from the main dapagliflozin also produce several other minor metabolites. These include a minor glucuronidated metabolite (about 5.4% of the total metabolism), a de-ethylated metabolite (less than 5% of the total metabolism) and a hydroxylated metabolite (also less than 5% of the total metabolism). Metabolism of dapagliflozin is facilated by various enzyme in the body, including cytochrome P-450(CYP) enzymes such as CYP1A1, CYP1A2, CYP2A6, CYP2C9, CYP2D6 and CYP3A4. Additionally, uridine diphosphate glucuronyltransferase (UGT) enzyme, specifically UGT1A9, UGT2B4 and UGT2B72 are involved in the glucuronidation process that leads to the formation of the major metabolite.

Route of elimination: 75.2% of dapagliflozin is eliminated through the urine and 1.6% of the dose in unchanged form. 21% of dose is excreted in the feces. Renal clearance: 5.6ml\min.

Parameter	**Value**
Bioavailability	Approximately 78%
Maximum Plasma Concentration (Cmax)	168-302 ng/mL
Time to Reach Maximum Concentration (Tmax)	1-2 hours
Protein Binding	Greater than 91%
Volume of Distribution	1182 L
Half-Life	12.9 hours
Clearance	15.7 L/hour

(Table.1)

Mechanism of action

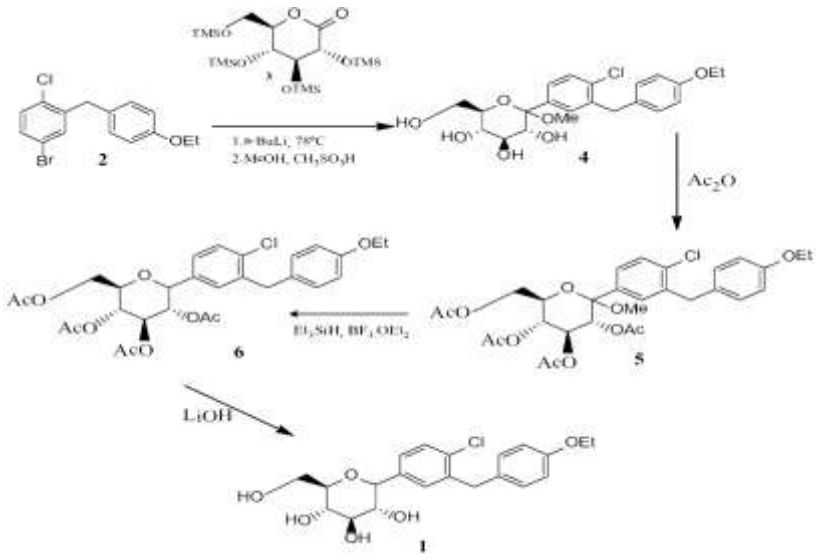
Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and its mechanism of action contains blocking the reabsorption of glucose in the kidneys.

1. **Normal Glucose Reabsorption:** In a healthy individual, the kidney filter glucose from the blood into the urine through specialized channels called SGLT 2 in the proximal tubules of the kidney. The filtered glucose is then reabsorbed back into the bloodstream through another set of channels called glucose transporters located in the proximal tubular cells.
2. **Inhibition of SGLT2**: Dapagliflozin acts by selectively inhibiting SGLT2, the primary glucose transporter responsible for glucose reabsorption in the kidney. By inhibiting SGLT2, dapagliflozin prevents the reabsorption of glucose back into the bloodstream.
3. **Increased Glucose Excretion**: As a result of SLGT2 inhibition, glucose remain in the urine rather than being reabsorbed. This leads to an increased excretion of glucose in the urine, a process known as glycosuria. By excreting excess glucose, dapagliflozin helps lower blood glucose level in individuals with type2 diabetes.
4. **Caloric Loss**: Since glucose is being excreted in the urine, dapagliflozin effectively reduce the number of calories absorbed from glucose, leading to a modest reduction in body weight in patients with type 2 diabetes.
5. **Additional Effects**: In addition to its glucose – lowering effects, dapagliflozin has been shown to have other beneficial effects. It can promote mild diuresis (increased urine production) and natriuresis (increased excretion of sodium), which may lead to modest reductions in blood pressure.

Methods of Synthesis

Scheme-1

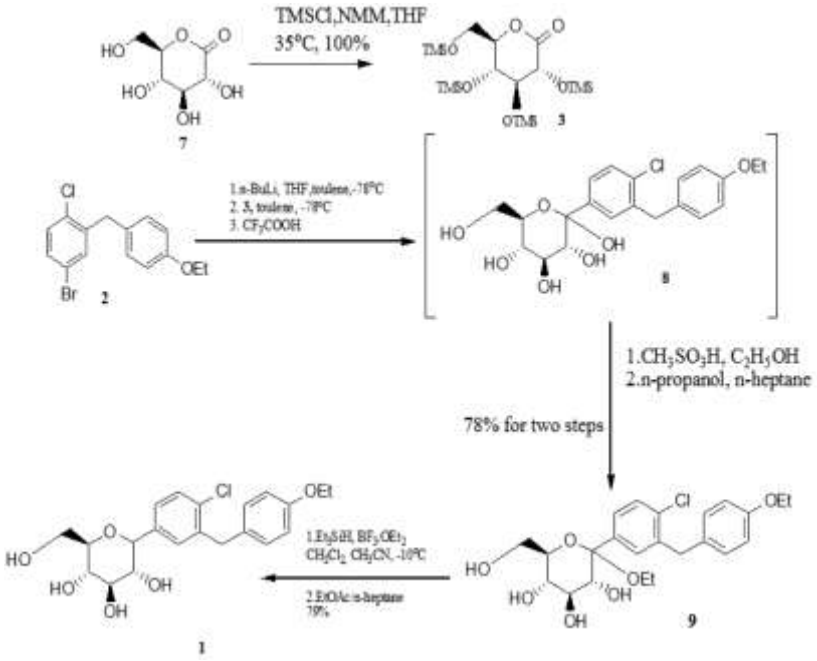
Scheme 1 shows the general synthetic of dapaglifozin. Gluconolactone 3 was treated with aryl lithium. Aryl lithium was produced by reacting aryl bromide 2 (by exchanging Li/Br) with n- Butyl lithium. Methyl C-aryl glucoside 4 was synthesized by reaction of produced mixture with methane sulfonic acid in the presence of methanol. Compound 4 was passed through acetylation in the presence of Ac_2O and led to formation of 5. Now reduction of 5 to 6 with the help of Et_3SiH and $BF_3.OEt_2$. Finally, dapaglifozin 1 was produced through hydrolysis of 6 by LiOH.



(Fig. 1.1)

Scheme-2

In the updated methodology scheme 2, a chemical called trimethylsilyl chloride was added to gluconolactone 7 in the presence of N-methylmorpholine and tetrahydrofuran (THF). This addition resulted in the formation of a compound known as persilyated lactone 3. Continuing the reaction, aryl bromide 2 was reacted with n-BuLi and added to the persilyated lactone 3. This led to the formation of an intermediate compound called lactol 8. The lactol 8 was produced by reacting the resulting reaction mixture with trifluoroacetic acid in the aqueous form. Subsequently, compound 8 was subjected to methane-sulfonic acid in ethyl alcohol, resulting in the production of ethyl C-aryl glycoside 9. The crude product 9 was obtained in the form of an oil after conducting solvent screening. Jun et al. reported that more than 98% pure compound 9 was obtained in the form of a crystalline solvate after crystallizing the crude oil from a mixture of n-propanol and n-heptane. Furthermore, Wang et al. proposed a method to achieve a high level of diastereoselectivity by reducing the tetra-O-unprotected methyl C-aryl glucoside using Et3SiH and BF3.Et2O. The resulting product is an amorphous foam, which is the active pharmaceutical ingredient (API) isolated after the reduction of compound 9. The production of a co-crystalline complex facilitates the isolation and purification of the API. In conclusion, it is found that more than 99.7% pure dapagliflozin, an active pharmaceutical ingredient, can be produced with an overall yield of 79% by crystallizing a mixture consisting of n-heptane and ethyl acetate.



(Fig. 1.2)

Medicinal Use

Dapagliflozin belongs to a class of drugs known as sodium-glucose co-transporter 2 (SGLT2) inhibitors. It is commonly used for the treatment of type 2 diabetes mellitus. Here are some details regarding the medicinal use of dapagliflozin:

Type 2 Diabetes Mellitus: Dapagliflozin is approved for the management of type 2 diabetes. It lowers blood sugar levels by inhibiting the reabsorption of glucose in the kidneys, following to increased urinary glucose excretion. By this dapagliflozin helps to improve glycemic control.

Glycemic Effect: Dapagliflozin with a proper diet and exercise, can help improve glycemic control in adults with type 2 diabetes Mellitus. It is prescribed in the form of adjunct to other antidiabetic medications like metformin.

Cardiovascular Avail: Dapagliflozin has shown cardiovascular benefits in patients with comorbid condition of type 2 diabetes and cardiovascular disease. Clinical studies have shown that it can reduce the risk of major cardiovascular events like cardiovascular death and stroke.

Heart Failure: Dapagliflozin has also been approved for the treatment of heart failure with reduced ejection fraction in adults, regardless of whether they have diabetes. It helps reduce the risk of hospitalization for heart failure and cardiovascular death in these patients.

Diabetic Kidney Disease: Dapagliflozin has shown efficacy in slowing the progression of diabetic kidney disease. It reduces the risk of worsening kidney function, end-stage renal disease and chronic kidney disease.

Adverse reaction

Less common Effects

Dapagliflozin can cause some common side effects that occur in more than 1 in 100 individuals. These side effects are mild and temporary.

1. Thrush: Some individuals may develop thrush, which is a fungal infection in the mouth or genitals.
2. Back pain: Dapagliflozin might occasionally cause back pain
3. Dizziness: Feeling dizzy can occur as a side effect. It's important to be cautious when getting up from a sitting or lying position to prevent falls
4. Mild skin rash: Some individuals may experience a mild skin rash
5. Cough
6. Weight gain

Low blood sugar

When dapagliflozin is taken in combination with other diabetes medications like sulfonylureas, there is a potential risk of your blood sugar dropping too low. This condition is known as hypoglycemia.

There are early warning signs that may indicate low blood sugar levels. These signs include hunger, trembling or shaking sensation, sweating, confusion, and not concentrating

It's worth noting that low blood sugar can also occur during sleep. If this happens, you may wake up feeling sweaty, tired, and confused. It's crucial to be cautious and monitor your blood sugar levels, even during sleep, to ensure they remain within a safe range.

Severe renal adverse effects

Typical therapeutic options for treating Type 2 diabetes (T2D) include several medications such as metformin, sulfonylurea, sitagliptin and insulin. However, more recently, a new class of drugs called sodium-glucose cotransporter-2 inhibitors (SGLT2i) has emerged as a treatment option for Type 2 diabetes. These medications, including empagliflozin and canagliflozin, work in the kidneys to help manage blood glucose levels.

In the kidneys, glucose is normally reabsorbed in the proximal tubule of the loop of Henle. The sodium-glucose cotransporter-2 protein, composed of 672 amino acids and located in the S1 segment of the proximal renal tubule, is responsible for this reabsorption. It specifically target this protein, preventing glucose reabsorption and promoting its excretion through urine. Dapagliflozin, one of the sodium-glucose cotransporter-2 inhibitors, has undergone extensive research in controlled clinical trials involving diabetic patients, either as a standalone treatment or in combination with other ant hyperglycemic agents. It has been approved by the US Food and Drug Administration (FDA) as a therapeutic option for Type 2 diabetes.

While sodium-glucose cotransporter-2 inhibitors have shown efficacy in managing blood glucose levels, one potential side effect is an increased risk of urinary tract infections. The underlying mechanism for this association is thought to be related to the presence of high glucose levels in the urine, which provides a favorable environment for bacterial growth. One study found that the levels of Escherichia coli, a common bacteria associated with UTIs, correlated with glucose levels.

The objective of the present study is to determine the frequency of UTIs in patients with Type 2 diabetes who are receiving dapagliflozin at doses of either 5 or 10 mg. By investigating this aspect, researchers aim to gain insights into the potential relationship between sodium-glucose cotransporter-2 inhibitor use and urinary tract infections in diabetic patients.

Treatment of overdose

Dapagliflozin is a medication used to treat type 2 diabetes by reducing blood sugar levels through increased urinary glucose excretion. In cases of overdose with dapagliflozin, it's important to seek immediate medical attention.

Some considerations for the treatment of dapagliflozin overdose:

1. **Contact emergency**: If you suspect an overdose, call any emergency number or poison management center right away. They will provide immediate guidance and may advise you to go to the nearest hospital.
2. **Supportive care**: In the hospital, medical professionals will focus on providing supportive care to stabilize the person's condition. This may involve monitoring vital signs like heart pulse, blood pressure, and blood glucose level and vitals.
3. **Gastric decontamination**: Depending on the situation, healthcare providers might consider gastric decontamination methods such as gastric lavage or administration of activated charcoal to help prevent further absorption of dapagliflozin from the gastrointestinal tract.
4. **Fluid and electrolyte management**: Dapagliflozin works by increasing urinary glucose excretion, which can lead to increased frequency of urine production and subsequent fluid and electrolyte imbalances. Healthcare professionals will closely monitor and manage the individual's fluid and electrolyte levels to ensure proper balance.

5. **Blood sugar monitoring**: It's important to regularly monitor blood glucose levels during an overdose situation. This allows healthcare providers to determine the severity of hypoglycemia and take appropriate measures to address it.
6. **Symptomatic treatment**: Treatment may involve addressing specific symptoms or complications that arise from the overdose. This could include managing low blood sugar, addressing dehydration, or providing supportive measures for any other related conditions.

Contraindications

Dapagliflozin is a medication used to treat type 2 diabetes to lower blood sugar levels. However, like any medication, it also has contraindications, which are specific situations in which its use is not recommended or should be approached with caution.

Type 1 diabetes: Dapagliflozin is not indicated for the treatment of type 1 diabetes, as it works by targeting the kidneys to reduce glucose reabsorption, which is not effective in patients with type 1 diabetes who are insulin resistant.

Diabetic ketoacidosis: Dapagliflozin is contraindicated in individuals with diabetic ketoacidosis, a condition showing high levels of ketones and acid in the blood. The drug may exacerbate this condition or increase the risk of developing it.

Severe kidney impairment: Dapagliflozin is primarily eliminated through the kidneys, so individuals with severe kidney impairment or end-stage renal disease may experience reduced drug clearance, leading to an increased risk of adverse effects.

Hypersensitivity: If someone has had a previous hypersensitivity or allergic reaction to dapagliflozin or any of its components, it is contraindicated to use this medication due to the risk of a severe allergic reaction.

Pregnancy and breastfeeding: The safety of dapagliflozin during pregnancy and lactation has not been established. It is generally recommended to avoid its use during these periods due to limited data on potential risks to the developing fetus or infant.

Children: Dapagliflozin is not recommended for use in children and adolescents under 18 years old, as its safety and efficacy have not been established in this population.

Interactions

One significant drug interaction to be aware of is with diuretics or medications that increase urine production. Dapagliflozin itself is a type of medication called a sodium-glucose co-transporter 2 (SGLT2) inhibitor, which works by increasing glucose excretion through the urine. When dapagliflozin is combined with other diuretics, like loop diuretics or thiazide diuretics, the risk of dehydration and low blood pressure may increase. It's important to monitor fluid balance and blood pressure closely in such cases.

Another important interaction involves insulin, which are medications that stimulate the pancreas to produce more insulin. Dapagliflozin can enhance the glucose-lowering effects of insulin, followed by an increased risk of hypoglycemia. Dose changes of these medications may be necessary to avoid this potentially dangerous side effect.

Additionally, certain medications that affect the kidneys, like nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors, may interact with dapagliflozin. These drugs can affect kidney function and may potentially reduce the effectiveness of dapagliflozin or increase the risk of kidney-related side effects. Close monitoring of kidney function is advisable when these medications are used together.

Conventional marketed formulation

Serial number	Dosage Form	Brand Name	Company Name	Dose	Price (Approximately in INR)
1	Tablet	Forxiga	AstraZeneca	5 mg, 10 mg	₹500-600 per month
2	Tablet(Extended-Release)	Xigduo XR	AstraZeneca	5 mg/500 mg,	₹600-700 per month
	(SGLT2 Inhibitor, and Metformin)			5 mg/1000 mg,	
				10 mg/500 mg,	
3	Tablet	Dapagliflo	Ajanta Pharma	10 mg	₹400-500 per month
4	Tablet (Extended-Release)	Qternmet XR	AstraZeneca	5 mg/500 mg/850 mg,	₹2,500-3,000 per month
	(SGLT2 Inhibitor, DPP-4 Inhibitor, and Metformin in Fixed-Dose Combination)			5 mg/1000 mg/850 mg,	
5	Tablet (SGLT2 Inhibitor and Saxagliptin)	Qtern	AstraZeneca	One tablet once daily	Varies (check locally)

(Table.2)

Novel marketed formulation

Brand Name	Company	Dosage Form	Strengths	Indication	Price (Approximately in INR)
Farxiga	Developed by Bristol-Myers Squibb in partnership with AstraZeneca.	Film-coated tablets	5 mg, 10 mg	Treatment of type 2 diabetes mellitus	₹392.70
Forxiga	Developed by Bristol-Myers Squibb in partnership with AstraZeneca.	Film-coated tablets	5 mg, 10 mg	Treatment of type 2 diabetes mellitus	₹500-600 per month

(Table.3)

Patents

Dapagliflozin is a medication used to treat diabetes, which is marketed under various brand names such as Farxiga in the US and Forxiga in the EU. It was created through a collaboration between Bristol-Myers Squibb and AstraZeneca. This drug is considered essential and is included in the World Health Organization's List of Essential Medicines. The current patent introduces an enhanced method for producing dapagliflozin, specifically following Formula (II). The process involves a step called hydrolysis, where a compound represented by Formula (III) is subjected to this reaction. What makes this method different and better is the inclusion of an amine base during the hydrolysis step. By utilizing an amine base, this invention improves the preparation process for dapagliflozin. This could potentially enhance the efficiency, yield, or quality of the final product compared to previous methods. The patent grants exclusive rights to the inventors for using this improved process for a certain period of time.

Invention of patents for preparation of formulation

Formula I

Several patents, namely U.S. Patent Nos. 6,515,117, 7,375,213, 7,932,379, and 7,919,598, have been granted for the formulation and preparation of dapagliflozin. These patents describe a method for producing dapagliflozin by hydrolyzing an acetylated form of the compound, denoted as Formula III, using alkali metal hydroxides like lithium hydroxide or sodium hydroxide. However, dapagliflozin obtained from these processes contains a notable impurity, which can be detected at a specific relative retention time (RRT) using high-performance liquid chromatography (HPLC).

The first patent is known as Indian Patent No. 205147, and the second patent is Indian Patent No. 235625.

Initially, Bristol Myers Squibb Company ("Bristol") held the registered patents for these two inventions. However, through an assignment deed dated 01.02.2014, Bristol transferred the rights of these patents to Astra Sweden. This means that Astra Sweden became the new owner and holder of the patents.

These patents are crucial because they grant exclusive rights to the patent holder to manufacture, sell, and distribute Dapagliflozin in India.

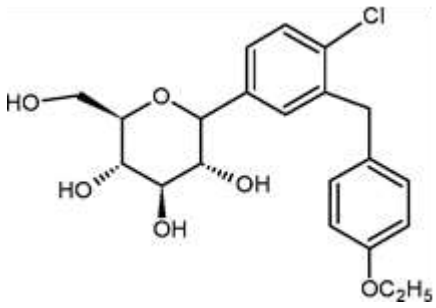
They provide legal protection to the patent holder, preventing others from producing and selling the drug without authorization.

The case likely involves a dispute or legal challenge related to these patents. It could potentially question the validity or infringement of the patents, or it may involve issues surrounding the transfer of rights from Bristol to Astra Sweden. Further details about the nature of the case would be needed to provide a more comprehensive understanding.

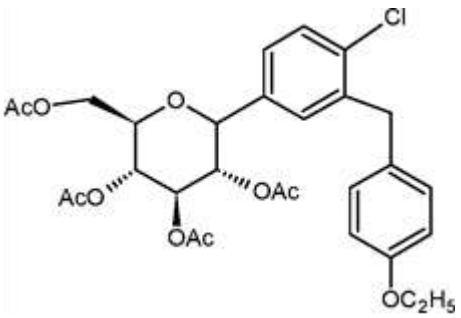
The current invention aims to address this issue by providing an improved process that reduces or eliminates the impurity associated with the manufacturing of dapagliflozin. The inventors have developed a method that specifically targets minimizing or removing this process-related impurity, thereby enhancing the quality and purity of the final product.

Summary of the Invention

A first condition of the present invention gives an improved process for the preparation of dapagliflozin of Formula II



Formula II (Fig.2.1)



Formula III (Fig.2.2)

The process has the step of hydrolyzing the compound of Formula III in the presence of amine base.

Year of grant and expiry of dapagliflozin:

- Firstly approved by the US food and drug administration (FDA) in 2014.
- Both, in 147 and in 625 were granted to Bristol Myers Squibb Company, which in February 2014, assigned the rights to AstraZeneca ab, Sweden. The dates of grant and expiry of in 147 are March 15, 2007 and October 2, 2020 and the dates of grant and expiry of in 625 are July 9, 2009 and May 15, 2023 respectively.

Bibliography

(1) Paik, J.; Blair, H. A. Dapagliflozin: A Review in Type 1 Diabetes. Drugs 2019, 79 (17), 1877–1884. https://doi.org/10.1007/s40265-019-01213-x.

(2) Dhillon, S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs 2019, 79 (10), 1135–1146. https://doi.org/10.1007/s40265-019-01148-3.

(3) Arow, M.; Waldman, M.; Yadin, D.; Nudelman, V.; Shainberg, A.; Abraham, N. G.; Freimark, D.; Kornowski, R.; Aravot, D.; Hochhauser, E.; Arad, M. Sodium–Glucose Cotransporter 2 Inhibitor Dapagliflozin Attenuates Diabetic Cardiomyopathy. Cardiovasc. Diabetol. 2020, 19 (1). https://doi.org/10.1186/s12933-019-0980-4.

(4) Kasichayanula, S.; Liu, X.; LaCreta, F.; Griffen, S. C.; Boulton, D. W. Clinical Pharmacokinetics and Pharmacodynamics of Dapagliflozin, a Selective Inhibitor of Sodium-Glucose Co-Transporter Type 2. Clin. Pharmacokinet. 2014, 53 (1), 17–27. https://doi.org/10.1007/s40262-013-0104-3.

(5) Farxiga (dapagliflozin) FDA approval history. Drugs.com. https://www.drugs.com/history/farxiga.html (accessed 2023-07-17).

(6) EMA. Forxiga. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga (accessed 2023-07-17).

(7) Mechanism of action (MOA). Farxiga-hcp.com. https://www.farxiga-hcp.com/mechanism-of-action.html (accessed 2023-07-17).

(8) PubChem Compound Summary for CID 9887712. National Center for Biotechnology Information 2023.

(9) Becker, A. API Co-Crystals - Trends in CMC-Related Aspects of Pharmaceutical Development beyond Solubility. Drug Discov. Today 2023, 28 (5), 103527. https://doi.org/10.1016/j.drudis.2023.103527.

(10) Europa.eu. https://www.ema.europa.eu/en/documents/assessment-report/forxiga-epar-public-assessment-report_en.pdf (accessed 2023-07-17).

(11) Dapagliflozin: Diabetic Ketoacidosis: Case Report. React. Wkly. 2017, 1662 (1), 129–129. https://doi.org/10.1007/s40278-017-33759-x.

(12) Watada, H.; Shiramoto, M.; Ueda, S.; Tang, W.; Asano, M.; Thorén, F.; Kim, H.; Yajima, T.; Boulton, D. W.; Araki, E. Pharmacokinetics and Pharmacodynamics of Dapagliflozin in Combination with Insulin in Japanese Patients with Type 1 Diabetes. Diabetes Obes. Metab. 2019, 21 (4), 876–882. https://doi.org/10.1111/dom.13593.

(13) Filippatos, T. D.; Liberopoulos, E. N.; Elisaf, M. S. Dapagliflozin in Patients with Type 2 Diabetes Mellitus. Ther. Adv. Endocrinol. Metab. 2015, 6 (1), 29–41. https://doi.org/10.1177/2042018814558243.

(14) Albarrán, O. G.; Ampudia-Blasco, F. J. Dapagliflozina, el primer inhibidor SGLT 2 en el tratamiento de la diabetes tipo 2. Med. Clin. (Barc.) 2013, 141, 36–43. https://doi.org/10.1016/s0025-7753(13)70062-9.

(15) Dapagliflozin, Aflibercept, Aripiprazole Recommended by NICE. PharmacoEconomics Outcomes News 2013, 680 (1), 14–14. https://doi.org/10.1007/s40274-013-0488-1.

(16) PubChem. Dapagliflozin. Nih.gov. https://pubchem.ncbi.nlm.nih.gov/compound/Dapagliflozin (accessed 2023-07-17).

(17) Balkanski, S. Dapagliflozin – Structure, Synthesis, and New Indications. Farmatsiia (Sofia) 2021, 68 (3), 591–596. https://doi.org/10.3897/pharmacia.68.e70626.

(18) Yu, J.; Cao, Y.; Yu, H.; Wang, J. A Concise and Efficient Synthesis of Dapagliflozin. Org. Process Res. Dev. 2019, 23 (7), 1458–1461. https://doi.org/10.1021/acs.oprd.9b00141.

(19) Dapagliflozin: a medicine used to treat type 2 diabetes. nhs.uk. https://www.nhs.uk/medicines/dapagliflozin/ (accessed 2023-07-17).

(20) DAPAGLIFLOZIN: Uses, side effects and medicines. Apollopharmacy.in. https://www.apollopharmacy.in/salt/DAPAGLIFLOZIN (accessed 2023-07-17).

(21) Side effects of dapagliflozin. nhs.uk. https://www.nhs.uk/medicines/dapagliflozin/side-effects-of-dapagliflozin/ (accessed 2023-07-17).

(22) Dapagliflozin (oral route). Mayoclinic.org. https://www.mayoclinic.org/drugs-supplements/dapagliflozin-oral-route/side-effects/drg-20095101 (accessed 2023-07-17).

(23) Farxiga (dapagliflozin) dosing, indications, interactions, adverse effects, and more. http://reference.medscape.com. https://reference.medscape.com/drug/farxiga-dapagliflozin-999899 (accessed 2023-07-17).

(24) Philip Thornton, D. Dapagliflozin. Drugs.com. https://www.drugs.com/dapagliflozin.html (accessed 2023-07-17).

(25) Dapagliflozin (Farxiga). Everydayhealth.com. https://www.everydayhealth.com/drugs/dapagliflozin (accessed 2023-07-17).

(26) Tirmenstein, M.; Dorr, T. E.; Janovitz, E. B.; Hagan, D.; Abell, L. M.; Onorato, J. M.; Whaley, J. M.; Graziano, M. J.; Reilly, T. P. Nonclinical Toxicology Assessments Support the Chronic Safety of Dapagliflozin, a First-in-Class Sodium-Glucose Cotransporter 2 Inhibitor. Int. J. Toxicol. 2013, 32 (5), 336–350. https://doi.org/10.1177/1091581813505331.

(27) Hall, V.; Kwong, J.; Johnson, D.; Ekinci, E. I. Caution Advised with Dapagliflozin in the Setting of Male Urinary Tract Outlet Obstruction. BMJ Case Rep. 2017, bcr-2017-219335. https://doi.org/10.1136/bcr-2017-219335.

(28) HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use FARXIGA safely and effectively. See full prescribing information for FARXIGA. FARXIGA ® (dapagliflozin) tablets, for oral use Initial U.S. Approval: 2014. Fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202293s015lbl.pdf (accessed 2023-07-17).

(29) Farxiga (dapagliflozin) dose, indications, adverse effects, interactions... from Pdr.net. Pdr.net. https://www.pdr.net/drug-summary/Farxiga-dapagliflozin-3427 (accessed 2023-07-17).

(30) Dapagliflozin interactions. Drugs.com. https://www.drugs.com/drug-interactions/dapagliflozin.html (accessed 2023-07-17).

(31) Dapagliflozin (oral route). Mayoclinic.org. https://www.mayoclinic.org/drugs-supplements/dapagliflozin-oral-route/before-using/drg-20095101 (accessed 2023-07-17).

(32) Scheen, A. J. Drug–Drug Interactions with Sodium-Glucose Cotransporters Type 2 (SGLT2) Inhibitors, New Oral Glucose-Lowering Agents for the Management of Type 2 Diabetes Mellitus. Clin. Pharmacokinet. 2014, 53 (4), 295–304. https://doi.org/10.1007/s40262-013-0128-8.

(33) Unnisa, A.; Chettupalli, A. K.; Al Hagbani, T.; Khalid, M.; Jandrajupalli, S. B.; Chandolu, S.; Hussain, T. Development of Dapagliflozin Solid Lipid Nanoparticles as a Novel Carrier for Oral Delivery: Statistical Design, Optimization, in-Vitro and in-Vivo Characterization, and Evaluation. Pharmaceuticals (Basel) 2022, 15 (5), 568. https://doi.org/10.3390/ph15050568.

(34) Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc). Org.uk. https://www.medicines.org.uk/emc/product/7607/smpc (accessed 2023-07-17).

(35) Dapagliflozin- a novel SGLT2 inhibitor. Slideshare.net. https://www.slideshare.net/shahjadaselim9/dapagliflozin-a-novel-sglt2-inhibitor (accessed 2023-07-17).

(36) Wikipedia contributors. Dapagliflozin. Wikipedia, The Free Encyclopedia. https://en.wikipedia.org/w/index.php? title=Dapagliflozin &oldid=1160703933 .

(37) How and when to take dapagliflozin. nhs.uk. https://www.nhs.uk/medicines/dapagliflozin/how-and-when-to-take-dapagliflozin/ (accessed 2023-07-17).

(38) Patel, S. Dapagliflozin patent case: Where is the unity?. Linkedin.com. https://www.linkedin.com/pulse/dapagliflozin-patent-case-where-unity-sanjaykumar-patel (accessed 2023-07-17).

(39) Samal, A. Dapagliflozin patent receives another blow: Same old coverage-disclosure story. Spicyip. https://spicyip.com/2021/08/dapagliflozin-patent-receives-another-blow-same-old-coverage-disclosure-story.html (accessed 2023-07-17).

(40) Cho, H. J.; Woo, M. R.; Cho, J. H.; Kim, Y., Il; Choi, H.-G. Novel Dapagliflozin Di-L-Proline Cocrystal-Loaded Tablet: Preparation, Physicochemical Characterization, and Pharmacokinetics in Beagle Dogs and Mini-Pigs. Pharm. Dev. Technol. 2022, 27 (3), 331–340. https://doi.org/10.1080/10837450.2022.2052320.

(41) Tentolouris, A.; Vlachakis, P.; Tzeravini, E.; Eleftheriadou, I.; Tentolouris, N. SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects. Int. J. Environ. Res. Public Health 2019, 16 (16), 2965. https://doi.org/10.3390/ijerph16162965.

(42) Plosker, G. L. Dapagliflozin: A Review of Its Use in Patients with Type 2 Diabetes. Drugs 2014, 74 (18), 2191–2209. https://doi.org/10.1007/s40265-014-0324-3.

(43) Mende, C. W. Chronic Kidney Disease and SGLT2 Inhibitors: A Review of the Evolving Treatment Landscape. Adv. Ther. 2022, 39 (1), 148–164. https://doi.org/10.1007/s12325-021-01994-2.

(44) Blair, H. A. Dapagliflozin: A Review in Symptomatic Heart Failure with Reduced Ejection Fraction. Am. J. Cardiovasc. Drugs 2021, 21 (6), 701–710. https://doi.org/10.1007/s40256-021-00503-8.

(45) Zhou, X.; Ye, X.; Guo, X.; Liu, D.; Xu, J.; Hu, F.; Zhai, Y.; Gao, Y.; Xu, X.; Dong, Z.; He, J. Safety of SGLT2 Inhibitors: A Pharmacovigilance Study from 2013 to 2021 Based on FAERS. Front. Pharmacol. 2021, 12. https://doi.org/10.3389/fphar.2021.766125.

(46) HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use FARXIGA safely and effectively. See full prescribing information for FARXIGA. FARXIGA ® (dapagliflozin) tablets, for oral use Initial U.S. Approval: 2014. Fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s020lbl.pdf (accessed 2023-07-17).