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A Systemic Review on Canagliflozin Impurities

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Abstract: The control of impurities in drug substance and drug formulation is critical concern in the pharmaceutical industry. The impurities are potent and cause serious toxic effects which are harmful to human health. The control of such impurities is mandatory for pharmaceuticals companies to get the regulatory approval of their pharmaceutical products. Hence the International Conference on Harmonization (ICH) and Food and Drug Administration (FDA) guidelines provide guidance to the industry for manufacturing high quality medicines. Canagliflozin is Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitor used in the treatment of type 2 diabetes. Canagliflozin is commercially available since 2013 in United states, Europe and it is included in the world health organization's essential medicines list. Canagliflozin is chemically D-glucitol compound comprising sugar moiety. This review aims to provide comprehensive overview of canagliflozin impurities and different analytical methods for detection.

Keywords: *Impurities, International Conference on Harmonization (ICH), Canagliflozin, SGLT Inhibitor.*

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I. INTRODUCTION

Impurities are undesirable chemicals present in the pharmaceutical compounds and formulations. Impurities are not of therapeutic importance, and they are harmful hence need to be identified and controlled. Most of the drug substances are prepared by synthetic routes by using different solvents and reagents. The residual solvents, trace amounts of inorganic, and organic components can be generated during synthesis of active pharmaceutical substances. The degradation products formed during process, storage, packaging components, effect of heat, light, oxidants may form impurities in drug products. These components may remain in the final product and are considered as impurities. The presence of impurities causes safety issues hence it is critical to identify and control in the drug substance and drug product. If the impurities are not controlled in the final drug product, then it may cause serious toxic effects to the patient. The level of impurities in pharmaceutical products is critical parameter to define the quality of drug products. The presence of impurities even in trace amounts may impact quality, safety and efficacy of drug products. Therefore, International Conference on Harmonization (ICH) and Food and Drug Administration (FDA) guidelines introduced the identification and qualification procedures for impurities, by using various analytical methods. As per ICH guidelines, impurities present in the new drug substance at a level greater than 0.1% and impurities in new drug products at a level greater than the identification thresholds (1% for a maximum daily dose of <1 mg to 0.1% for a maximum daily dose of >2g) should be described.

Further understanding the source of impurity formation in drug substances and drug product is the essential step in drug development and regulatory assessment. Hence it is necessary to study the chemistry of drugs and possible impurity formation routes while drug development and formulation development. The entire process of identification, characterization, and quantification of known and unknown impurities in drug substances and drug products is known as impurity profiling. [1-4]

The present review reveals the impurity profiling of antidiabetic drug canagliflozin. Canagliflozin is the first antidiabetic drug that belongs to Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitor class. It is commercially available as oral tablet under the brand name INVOKANA by Janssen Pharmaceuticals. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus, to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) and to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day. The prevalence of diabetes worldwide is

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rising rapidly and is estimated to reach 4.4% of the world's population or approximately 366 million people by 2030. The long-term manifestations of diabetes contribute to its status as a leading cause of premature illness and mortality worldwide. [5]

➢ *Chemistry and Structure of Canagliflozin:*

The active ingredient present in the approved INVOANA tablet is Canagliflozin hemihydrate. Canagliflozin hemihydrate is a white to off-white powder, practically insoluble in water and freely soluble in ethanol and non-hygroscopic. Canagliflozin exhibits stereoisomerism due to the presence of five chiral centres. The diastereomeric purity of the drug substance is controlled by an achiral assay/purity high performance liquid chromatography (HPLC) method. Canagliflozin exibits polymorphism, form I is a hemihydrate, and an unstable amorphous Form II. Form I is present in the approved composition of INVOKANA tablet as active pharmaceutical ingredient. Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9. The chemical name of canagliflozin hemihydrate is (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2thienyl]-methyl]-4-methylphenyl]-D-glucitol hemihydrate. The CAS number is 842133-18-0, and the structural formula is shown in figure 1. [5, 6]

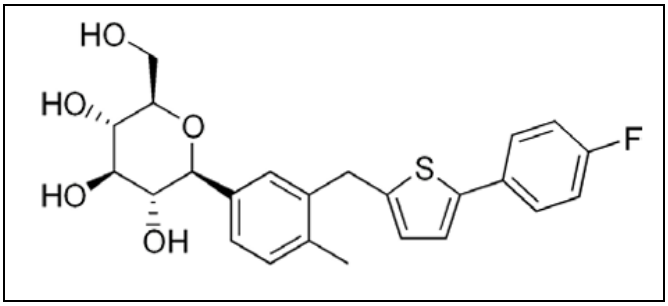

Fig 1 Chemical Structure of Canagliflozin

➢ *Canagliflozin Regulatory Approval Details:*

Canagliflozin is approved as tablet (100mg & 300mg) in United States, Europe, Australia, Canada, India and other countries under brand name INVOKANA to Janssen Pharms.

➢ *Canagliflozin patent status in US & India:*

There are three patents listed in orange book as on Jun 03, 2026, against Canagliflozin (INVOKANA) tablet in US.

- US7943788 (Expiry date: Jan 14, 2028) – claims Glucopyranoside compound Markush structure which covers the Canagliflozin compound or drug substance.
- IN232231 (Expired on Jul 30, 2024) – claims compound canagliflozin
- US7943582 (Expiry date: Aug 26, 2029): claims crystalline form of canagliflozin hemihydrate.
- US8513202 (Expiry date: Jun 03, 2028): claims crystalline form of canagliflozin hemihydrate.
- IN286412 (Expiry date: Dec 03, 2027): claims crystalline form of canagliflozin hemihydrate.

Canagliflozin is protected by compound patent till Jan 14, 2028 in United States and compound patent is expired in India. [7]

II. CANAGLIFLOZIN INMUPIRITIES AND THEIR FORMATION

➢ *Types of Canagliflozin Impurities*

Canagliflozin impurities primarily include process-related compounds, degradation products (dimer, sulfones, hydroperoxides), ring-opening impurities, and stereo isomers. The key impurities include the Canagliflozin dimer, peroxide impurity and furanose isomer. Canagliflozin hydroperoxide impurities are formed during storage.

➢ *Impacts of Canagliflozin Impurities*

Canagliflozin impurities, which can arise during synthesis, storage, or degradation, pose significant risks to both the pharmacological efficacy and safety of the medication. The presence of impurities, particularly polymorphic impurities such as anhydrous (An-CFZ) and monohydrate (Mono-CFZ) forms, can alter the drug's solubility and stability. These transformations can impair the pharmacokinetic profile (bioavailability) of the medication, potentially reducing its effectiveness in controlling blood sugar levels.

➢ *Potential Toxicity and Safety Risks:*

- *Genotoxic Impurities:* Specific impurities, such as hydroperoxide (Impurity-D), have been identified as potentially genotoxic, requiring strict control at trace levels (e.g., 5.0 ppm) to ensure they fall within safe regulatory limits.
- *Degradation Product Toxicity:* Oxidative degradation products, designated as DP1 and DP2, have been found to cause potential skin sensitization, while other degradation products (DP3 and DP4) may cause ocular irritation.
- *Nephrotoxicity Concerns:* Certain degradation products, such as melamine (associated with the combined drug metformin), have been linked to crystalluria, which can cause chronic kidney inflammation and renal failure.

➢ *Canagliflozin Impurities & their Formation Pathetways:*

- *Canagliflozin Acetyl Impurity:* This impurity is process impurity (i.e. intermediate stage) can be formed by acetylation of canagliflozin intermediate.
- *Canagliflozin Sulfone Impurity-(Impurity-F):* It is a known degradation product synthesized for analytical characterization. It is typically produced via the oxidation of canagliflozin or its intermediates using oxidizing agents like chloroperoxybenzoic acid (CPBA) resulting in the oxidation of the thiophene sulfur to sulfone.
- *Canagliflozin Keto Impurity:* This is a significant process-related impurity. It is a key degradation or process-related impurity that arises during the synthesis and storage of Canagliflozin active pharmaceutical ingredient (API).
- *Canagliflozin Hydroxy Impurity:* This is a degradation product or process-related impurity associated with the synthesis of the API Canagliflozin. This impurity contains a hydroxyl group added to the carbon bridging the phenyl and thiophene rings, often classified as a "ring opening" or hydroxy derivative.

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- *Canagliflozin KGL C Impurity (Canagliflozin Furanose Impurity):* This is a stereoisomeric impurity that typically arises during the synthesis of the active pharmaceutical ingredient (API) High acidic condition during the deprotection, or crystallization can promote the isomerisation that leads to this specific impurity.
- *Canagliflozin KGL D Impurity:* This is Canagliflozin desfluoro impurity, a structural analogue of Canagliflozin where the fluorine atom on the phenyl ring is absent. The synthesis typically involves the coupling of a sugar moiety with a diarylmethane component, followed by deprotection.
- *Canagliflozin KGL K Impurity:* This is also known as Monoacetyl Canagliflozin, typically occurs during the chemical synthesis of the API. This impurity is classified as a process impurity and is often a remnant or byproduct of specific protection/deprotection steps in the manufacturing route.
- *Canagliflozin KGL B Impurity:* The canagliflozin open-chain hydroxy impurity is formed during API synthesis primarily through incomplete cyclization or premature ring-opening of the glucosylated intermediate. This impurity occurs during the final stages of the synthesis, specifically during the reduction of gluconolactone intermediate or the subsequent deprotection steps. [8-13]

III. DETECTION AND QUANTIFICATION GENERAL METHODS OF IMPURITIES

Detection and quantitation of known and unknown impurities in drug substance and drug products is most critical and challenging step to ensure quality of the drug substance and drug product. Characterization of impurities is multistep process which involves separation, detection, identification, isolation, synthesis and structural elucidation by different methods. The several methods can be used individually or in combination such as UV Spectroscopy, Mass Spectrometry (MS), Infrared (IR), Nuclear Magnetic Resonance (NMR), Liquid chromatography (LC), High performance liquid chromatography (HPLC), Hyphenated techniques such as LC-MS, LC-MS/MS, Thin layer chromatography (TLC), Gas liquid chromatography (GLC), High Performance Thin Layer Chromatography (HPTLC) and Electrophoresis. The characterization of impurities is combinatorial efforts of organic scientists, formulation scientists and analytical scientists. [14-15]

IV. CONCLUSION

Drug impurity profiling is essential step in the drug development process. Impurity spectrum identification and control is the crucial step to ensure the quality of the drug. If known and unknown impurities are present in trace amount will cause safety concern and prone regulatory challenges for drug approval process. Canagliflozin is first SGLT-2 class D-glucitol compound used as antidiabetic agent. Canagliflozin compound forms several impurities include process-related compounds, degradation products (dimer, sulfones, hydroperoxides), ring-opening impurities, and stereo isomers. These impurities may cause significant risks on efficacy and safety of the drug product. Hence the present review provides systemic concise guide to the researchers on canagliflozin impurity formation paths, types and its detection method. Continued research and development is needed in the field of impurity profiling for identification of known and unknown impurities for the development of safe and effective medicines.

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