International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 11, November 2024 **ijppr.humanjournals.com** ISSN: 2349-7203

Bexagliflozin: A Review on Analytical Method Development and Validation for Quantification in Bulk and Pharmaceutical Dosage Form by Various Analytical Techniques

Mr.Gunasekaran P*, Dr.Priyadharshini R[1], Ms.Yamuna V[2], Mr.Yogesh Chhippa R[3]

[1]Assistant Professor, College of Pharmacy, Madras Medical College, Chennai. India.

[*,2,3]Post Graduate Student, Department of Pharmaceutical Chemistry. College of Pharmacy, Madras Medical College, Chennai, India.

Received: 2024-11-15 Revised: 2024-11-26 Accepted: 2024-11-28

ABSTRACT

Bexagliflozin is a recently authorised oral SGLT2 inhibitor that treats type 2 diabetes and shows potential in the fight against chronic kidney disease. We have thoroughly examined the literature from numerous analytical and pharmaceutical chemistry journals. We have also examined instrumental analytical techniques developed and applied to identify a drug in biological fluids, formulations, and bulk drugs, either alone or in combination with other drugs. The most recent analytical techniques that were reported are covered in this overview.

Keywords: Bexagliflozin, T2DM, Method development, validation.

INTRODUCTION

Bexagliflozin, marketed under the brand name Brenzavvy, is an antidiabetic drug that helps people with type 2 diabetes (T2D) improve their glycaemic control when combined with exercise and a nutritious diet. It is a sodium–glucose cotransporter-2 (SGLT2) dietary inhibitor. Relatively recently developed glucose-lowering drugs called SGLT2 inhibitors have several beneficial effects, including decreasing blood pressure and aiding in weight loss. One potent oral SGLT2 inhibitor is bexagliflozin. TheracosBio is developing it for two conditions: essential hypertension and type 2 diabetes. In order to improve glycaemic control in individuals with type 2 diabetes, it was first approved in the USA to be used in conjunction with diet and exercise. Dialysis patients, those with type 1 diabetes, and people whose glomerular filtration rate is expected to be less than 30 mL/min/1.73 m2 should not use bexagliflozin. The development of bexagliflozin for the treatment of essential hypertension is underway in the USA.[1] A cyclopropyloxyethoxy group at the para position of the peripheral phenyl ring sets bexagliflozin apart structurally from other SGLT2 inhibitors. A novel SGLT2 inhibitor bexagliflozin has shown promise in lowering blood glucose levels. SGLT2 inhibitors have been used in numerous studies to treat heart disease and, albeit not yet shown, a slowdown in the progression of Chronic Kidney Disease. In addition to its antihyperglycemic actions, bexagliflozin can produce albuminuria, reduced eGFR, and lower systolic blood pressure. Bexagliflozin, as it is currently marketed, may be seen as a promising choice due to its affordability, effectiveness, and safety.[2]

Description of drug [3][4]

Generic name: Bexagliflozin [*BEX-a-gli-FLOE-zin*]
Brand name: Brenzavvy
Chemical Formula : $C_{24}H_{29}ClO_7$
Dosage form: oral tablet (20 mg)
Drug class: SGLT-2 inhibitors

Weight :

Average: 464.94
Monoisotopic: 464.160181

Regulatory approval FDA approval date: January 20, 2023

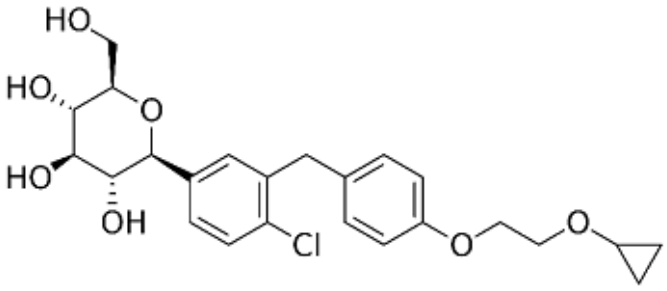

Figure No-1 Structure of Bexagliflozin

Chemical Taxonomy [2]

This compound is a member of the phenolic glycoside class of organic chemicals. These are organic substances that have a glycosyl moiety joined to a phenolic structure. Flavonoids and lignans are two types of phenolic structures. Natural glycosides contain a number of sugar units, including D-glucose, L-fructose, and L-rhamnose.

Kingdom: Organic compounds

Super Class: Organic oxygen compounds

Class: Organooxygen compounds

Sub Class: Carbohydrates and carbohydrate conjugates

Direct Parent: phenolic glycoside

Molecular Framework: Aromatic heteromonocyclic compounds

Pharmacodynamics

Adults with type 2 diabetes mellitus and healthy subjects who received one or more doses of bexagliflozin experienced dose-dependent increases in urine volume and urinary glucose excretion (UGE). Near-maximal UGE can be achieved with a dose of 20 mg of bexagliflozin, and multiple doses of the medication maintain elevated UGE values. Five times the recommended dosage of bexagliflozin does not result in clinically significant QTc interval prolongation.

Ketoacidosis, volume depletion, urosepsis, pyelonephritis, necrotising fasciitis of the perineum, and genital mycotic infections are risk factors for bexagliflozin use. Additionally, compared to patients getting a placebo, those treated with bexagliflozin have a higher risk of lower limb amputation. Furthermore, bexagliflozin usage may raise the risk of hypoglycemia in patients receiving insulin and insulin secretagogues.[5]

Pharmacokinetics [2]

C_{max}: 134 ng/mL

T_{max}: 2–4 h

AUC: 162 ng·hr/mL

Distribution:

Volume of distribution: 262 L

Plasma Protein Binding: 93%

Metabolism:

Major metabolism is glucuronidation via UGT1A9 to form pharmacologically inactive 3'-O glucuronide and oxidation via CYP3A4 to form oxidized metabolites of bexagliflozin.

Elimination:

Oral Bioavailability: ~78%

Half Life: 12 h Fecal ~51% (parent compound 28.7%), Renal ~41% (1.5% parent and 30.1% EGT0002149)

Clearance: 19.1 L/hr

Mechanism of Action [4][5]

Bexagliflozin is an extremely selective inhibitor of the sodium–glucose co-transporter 2 (SGLT2). The proximal renal tubule, which is where the majority of reabsorption occurs in the kidney, contains SGLT2, which transports sodium and glucose from the tubular lumen to the epithelium. By blocking SGLT2, bexagliflozin decreases the kidney's ability to reabsorb glucose and encourages its excretion in urine. Bexagliflozin, therefore, lowers blood glucose levels in patients with type 2 diabetes mellitus (T2DM) regardless of insulin sensitivity.

Bexagliflozin may cause serious side effects. [3]

- bladder infection
- low blood sugar--headache,
- drowsiness,
- fast heart rate,

Common side effects of bexagliflozin may include: [3]

- increased or urgent need to urinate large amounts or at night;
- pain and burning when you urinate; or
- vaginal itching or discharge.

Drug Interactions [6]

Using this medicine with any of the following medicines is usually not recommended, but may be required in some cases. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines.

- Chlorpropamide
- Glimepiride
- Glipizide
- Gliquidone

- Glyburide
- Insulin
- Insulin Aspart, Recombinant
- Insulin Bovine
- Insulin Degludec
- Insulin Detemir
- Insulin Glulisine
- Insulin Lispro, Recombinant
- Lithium
- Metformin
- Nateglinide
- Repaglinide
- Tolazamide
- Tolbutamide

Other Medical Problems [6]

The presence of other medical problems may affect the use of this medicine. Make sure you tell your doctor if you have any other medical problems, especially:

- history of Alcohol abuse
- Decrease in eating due to surgery or illness
- severe Dehydration
- history of Pancreatic insulin deficiency
- Weakened physical condition (due to illness or surgery)—May increase risk for more serious side effects.
- Blood vessel disease
- Diabetic foot ulcer
- Leg amputation (leg removal surgery),
- history of Neuropathy (nerve problem) of the leg—May increase the risk of leg amputations.
- Dehydration
- history of Genital yeast (fungus) infection (eg, balanitis, balanoposthitis, vulvovaginitis)
- Hypotension (low blood pressure)

- Hypovolemia (low blood volume)
- Kidney disease
- history of Urinary tract infections (eg, pyelonephritis, urosepsis)
- Diabetic ketoacidosis (high ketones and acid in the blood)
- Kidney disease, moderate to severe
- Liver disease - severe
- Type I diabetes—Should not be used in patients with these conditions.
- Fever
- Infection
- Surgery
- Trauma—Use with caution. These conditions may cause problems with blood sugar control.

Dosing [6]

For oral dosage form (tablets):

- Adults—At first, 20 milligrams (mg) once a day, taken in the morning.
- Children—Use and dose must be determined by your doctor.

Analytical Method Validation

Validation is a method-based approach to ensure a method's suitability as a quality control tool for analytical measurements. Any analytical measurement's goal is to produce accurate, dependable, and consistent results. The use of validated analytical techniques is crucial to accomplishing this objective. An analytical method consists of techniques, methods, procedures, and protocols. Analytical method validation includes the determination of accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness. The results from method validation can be used to moderate the quality, reliability, and consistency of analytical results, which is an integral part of any good analytical practice. The majority of laws and standards of quality governing laboratories also entail the validation of analytical procedures.

Reported Methods for bexagliflozin

Deepak Kumar Basedia et al (2024) work on the development and validation of a stabilityindicating reverse-phase high-performance liquid chromatography (RP-HPLC) method for accurately estimating Bexagliflozin in a commercial formulation.They proposed an RP-HPLC method that exhibits stability indicating characteristics, allowing for the assessment of drug integrity in the presence of probable degradants. The method was effectively used to quantify Bexagliflozin in a commercially accessible formulation, establishing a dependable tool for routine quality control examination. [7]

Satyajit raj nethekar et al. (2024) devised a green, ecologically friendly, fast, sensitive, costeffective, stability-indicating, and analyst-friendly method for evaluating bxf in pharmaceutical dosage form using a reverse phase-uplc technique. The method's specificity was achieved in an analytical column x-bridge (100 mm x 2.1 mm, 3.5 m) using a suitable mobile phase of 10mM Ammonium acetate and Methanol in a (55:45 v/v) ratio. The flow rate is 0.2 ml per minute. The injection volume is 1 µl, uv detection wavelength is 220 nm, and the run time is 2.5 minutes. The technique's robustness was evaluated using the QbD tool to create DoE's and analyze their robustness. The technique was shown to be linear between 25% and 150% concentration. The recovery was carried out from 50% to 150% level concentration, and the average recovery was discovered to be satisfactory. The deterioration and validation study results demonstrate that it is stable. As a result, this technique can be applied to pharmaceutical r&d and quality control departments. [8]

Bindhu M et al (2024) discovered a new, precise, and sensitive reversed-phase highperformance liquid chromatography (RP-HPLC) analytical method for quantifying bexagliflozin. They aer using a photo diode array detector for analysis and the analyzed compounds were separated using a Discovery® C18 (5 µm particle size, L × I.D. 15 cm × 4.6 mm) analytical column. The drugs were determined within 6.0 min using phosphate buffer (4.2ph_dipotassium hydrogen phosphate 0.01N) in water and Methanol in isocratic elution mode at a flow rate of 1.0 ml/min and temperature was maintained at 30°C. The optimal wavelength chosen was 220.0nm. Bexagliflozin had a retention time of 2.167 minutes. The calibration curve was linear from 5 to 30 µg/ml. The method's accuracy and precision were within acceptable limits of ±20% at the lower limit of quantitation and ±15% at other concentrations. All results were acceptable, confirming the method's suitability for routine quality control and drug assays. [9]

Yenduri Suvarna et al (2024) uses a computational chemistry with the purpose of optimizing the chromatographic column for the detection of certain pharmaceuticals such as Tapinarof, Elacestrant, and Bexagliflozin by means of studying the degree of intermolecular interactions between chemicals and stationary phases, For this purpose Avogadro with orca software was utilized to calculate the Gibbs free energy between the stationary phase and the pharmaceutical of choice for different columns, including C8 and C18. The tool was utilized for the purpose of optimizing the column in order to minimize the amount of solvent that was utilized and time to lessen the complexity of the procedure. Gibbs free energies of the complexes of Bexagliflozin and C8 was found to be -3193.16 Eh Gibbs free energy (hatree) , Binding free energy -268.63 KJ/mol. Gibbs free energies of the complexes of Bexagliflozin and C18 was found to be -3585.57 Eh Gibbs free energy (HATREE), Binding free energy - 149.34 KJ/mol . from this study C18 is the most suitable column for Bexagliflozin is identified. [10]

Kanaka Durga Valli A.et al. (2023) developed A simple, accurate, and exact approach was devised for the simultaneous estimate of bexagliflozin. Discovery C18 150 x 4.6 mm, 5m chromatogram analysis. The column was pumped at 0.9ml/min with a mobile phase consisting of 0.01N Na_2HPO_4 and Methanol 55:45. This buffer was 30 degrees Celsius. The optimal wavelength is 220.0nm. Bexagliflozin retained 2.854 minutes. The method precision was 0.4, and Bexagliflozin's percentage RSD was 0.9. Bexelifluzin recovered 99.63%. In the regression equation, Bexagliflozin's LOD and LOQ were 0.440 and 1.33. The Bexagliflozin regression equation is y = 2121x + 4049.8. Reduced retention and run times made the approach simple and cost-effective for conducting routine quality control tests in industries. [11]

Pusuluri Siva Krishna et al (2023) reviewed a variety of methods available for quality control of newly approved FDA medications such as Bexagliflozin, Daprodustat, Valmanasealfa-tycv, Sparsentan, Ritonavir. Bexagliflizolin was anlysed using muliple methods which are listed in the table below. [12]

DRUG	DRUG	DESCRIPTION	
Bexagliflozin	HPLC	System used	Agilent 1100 liquid chromatographic system
		Column used	CapcellpakC18MG column (100×4.6mm,5 µm, shiseido, Tokyo, Japan
		Mobile phase	Acetonitrile: Methanol: Water:10mM Ammonium acetate (450:275:275:5.5 v/v/v/v)
		Flow rate	0.7 mL/min
		Injection volume	10 µL
		MS detection technique employed	API 4000 triple quadrupole mass spectrometer
	LC-MS /MS	System used	Shimadzu LC – 20A liquid chromatography system
		Column used	Waters Nova- pak C18 (150×3.9mm,4µm) column
		Waters Nova- pak C18 (150×3.9mm,4µm) column	A : 0.1% formic acid in 0.5mM NH4 Ac under positive mode and 5mM NH4Ac under negative mode B : 0.1% formic acid in mixture of acetonitrile /methanol (50/50) The fraction of A was 85% to 2min ,50% to 4.5 min and 15% to 5.6 min, thereafter 85% to 8 min
		Flow rate	0.8 mL /min
		Injection volume	10 µL
		Mass spectrometric detection	API 4000 LC-MS/MS Mass spectrometer
		Column temperature	25°C

	UPLC	System used	UPLC-Q/TOF MS system for analysis on a waters ACQUITY UPLC system (water corporation, Milford, MA)
		Column used	ACQUITY HSS T3 C18 column with 1.7 µm particle size (100×2.1mm)
		Mobile phase	A: 10 mM Ammonium acetate B: Acetonitrile with 0.05% formic acid
		Flow rate	0.5mL /min
		Injection volume	10 µL
		Run time	20 min
		Detection technique	Synapt Q- TOF MS
		Column temperature	40℃

Tejaswi Gilakamsetti .et al. (2024) study has developed a straightforward, yet incredibly accurate, fast, and precise stability-indicating RP-HPLC method to measure the amount of Bexagliflozin in the pharmaceutical dosage form. The chromatographic elution was carried out on a reverse phase Discovery C18 column (150 x 4.6 mm, I.D. 5µm) with a mobile phase consisting of 0.01N Na2HPO4: CH2OH (55:45 v/v), which was prepared with 0.1% orthophosphoric acid to bring the pH down to 4.0. The flow rate was 0.9 mL min-1, and a photodiode array detector operating at 220 nm was used for analysis. Bexagliflozin's retention time was precisely determined to be 2.724 minutes. Throughout the concentration range of 5–30 µg mL-1, the drug showed linearity (R2 0.999). The findings indicated that the LOQ was 0.011µg mL-1 and the LOD was 0.004µg mL-1. Forced degradation was performed in accordance with ICH Q1A (R2) guidelines, and the developed method was validated to meet ICH requirements. Bexagliflozin can now be accurately quantified using a new stability-indicating RP-HPLC method. Regular analyses of bexagliflozin in both its pure form and pharmaceutical formulations were successfully conducted using the recommended methodology. [13]

Acknowledgements

We express our sincere thanks to the Department of Pharmaceutical Chemistry, College of Pharmacy, Madras Medical College (MMC), Chennai for providing necessary facilities for the research work.

Conflicts of Interest

The author declares there is no conflict of interest.

References

1. Dalal, Deepak; Kant, Ravi; Attri, Kavita; Kapoor, Garima1; Nagarajan, Kandasamy1; Bhutani, Rubina2; Sharma, Kiran3; Kaushik, Ujjawal4; Yadav, Mandeep; Jamwal, Neetu Singh5. A Systematic Overview of Bexagliflozin: A Type 2 Diabetic Drug. Asian Journal of Pharmaceutical Research and Health Care 15(2):p 109-114, Apr–Jun 2023. | DOI: 10.4103/ajprhc.ajprhc_25_23
2. Bassett, R.L., Gallo, G., Le, KP.N. *et al.* Bexagliflozin: a comprehensive review of a recently approved SGLT2 inhibitor for the treatment of type 2 diabetes mellitus. *Med Chem Res* 33, 1354–1367 (2024). https://doi.org/10.1007/s00044-024-03274-4
3. https://www.drugs.com/mtm/bexagliflozin.html
4. FDA Approved Drug Products: BRENZAVVY (bexagliflozin) tablets for oral use
5. Cowie MR, Fisher M: SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol. 2020 Dec;17(12):761-772. doi: 10.1038/s41569-020-0406-8. Epub 2020 Jul 14.
6. https://www.mayoclinic.org/drugs-supplements/bexagliflozin-oral-route/description/drg-20544720
7. Sandeep Kumar Tiwari*, Deepak Kumar Basedia, Vivek Thakur, B. K. Dubey. STABILITY INDICATION RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF BEXAGLIFLOZIN IN MARKETED FORMULATION. Zenodo; 2024.
8. Nethekar MS, Kanuparthy PR, Chintala V, Bhukya MV, Kowtharapu LP, Katari NK. Heptad Green Metrics and Quality by Design Tool Evaluated UPLC Content Determination Method for Bexagliflozin in Formulation Product. Available at SSRN 4726796
9. Bindu M. QUANTITATIVE DETERMINATION OF BEXAGLIFLOZIN IN TABLET FORMULATION AND BULK BY USING RP-HPLC. World Journal of Pharmaceutical Sciences. 2024 Jul 3.
10. Koppuravuri NP, Yenduru S, Shifa KM. Determining binding free energy by computational modelling: A theoretical approach for selection of stationary phase in chromatographic studies. Turkish Computational and Theoretical Chemistry.;9(1):41- 52.
11. Valli AK, Deepika DS, Kumar KA. ESTIMATION OF BEXAGLIFLOZIN BY USING RP-HPLC METHOD. World Journal of Pharmaceutical Sciences. 2023.

12. Krishna PS, Eswarudu MM, Babu PS, Likhitha T, Venkatesh N, Poojitha C, Sujana K, Gopaiah B. A review on analytical profile for newly FDA approved drugs in 2023.
13. Tejaswi Gilakamsetti, Poojitha Nalluri, Ramya Kuber Banoth. Development and Validation of a Novel RP-HPLC Method for Estimation of Bexagliflozin in Pure and Pharmaceutical Formulation. Research Journal of Pharmacy and Technology. 2024; 17(10):4758-4. doi: 10.52711/0974-360X.2024.00733 Available on : http s://www.rjptonline.org/AbstractView.aspx?PID=2024-17-10-18

How to cite this article:
Mr.Gunasekaran P et.al. Ijppr.Human, 2024; Vol. 30 (11): 278-285

Conflict of Interest Statement: All authors have nothing else to disclose.