Current Perspectives on Analytical Method Validation of Empagliflozin: A Comprehensive Review

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DOI: https://doi.org/10.51244/IJRSI.2026.1304000126

Received: 17 April 2026; Accepted: 22 April 2026; Published: 06 May 2026

ABSTRACT

Empagliflozin is an oral hypoglycemic drug belonging to the class of SGLT2 inhibitors. It acts on transporters in the proximal tubules of the kidneys to reduce blood glucose by promoting glucose excretion in the urine. This review examines various analytical method development strategies for Empagliflozin, with a focus on Quality by Design (QbD) approaches.

Keywords: Empagliflozin, Antidiabetic Drug, Analytical Method, QbD, ICH.

INTRODUCTION

The development and validation of analytical methods are fundamental to pharmaceutical research development. Choosing the right method requires taking into account several key factors, such as accuracy precision, sensitivity, selectivity, robustness, and ruggedness.

Empagliflozin is an oral glucose-lowering drug that was approved and came into clinical use in 2014. (Ndefo, U.A. (2015) It belongs to the sodium-glucose cotransporter 2 (SGLT2) inhibitor group. (Chen, L.H. (2013), (Scheen, A.J. (2014) These medications introduced for the treatment of the type 2 diabetes mellitus (T2DM). (Chawla, G. (2019) By potently blocking glucose reabsorption in the proximal tubule, it increases urinary glucose excretion. (Chen, L.H. (2013), (Chatterjee, (2016) Among the currently used or tested SGLT2 inhibitors, empagliflozin has the highest selectivity for SGLT2 over sodium–glucose cotransporter 1 (SGLT1). Benefits of empagliflozin administration reduction in body weight, blood pressure reduce & increase urinary excretion**,** Insuline resistance**,** Improve Glycemic control**,** Glucotoxicity reduction.

Different analytical techniques—including High-Performance Liquid Chromatography (HPLC), High Performance Thin-Layer Chromatography (HPTLC), UV-Visible spectrophotometry, and Liquid Chromatography–Mass Spectrometry (LC-MS) is widely used for its analytical capabilities. When combined with the appropriate measures. These techniques ensure accurate, precise, and reliable results, making them highly effective for method validation for routine quality control in pharmaceutical applications.

In analytical method consists of practical considerations, such as sample availability. The concentration of the analyte, time constraints, cost, and access to appropriate equipment also play a crucial role in this decision-making process.

Quality by Design (QbD)

The International Conference on Harmonisation (ICH) formulated recommendations for risk assessment,

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue IV April 2026

quality by design (QbD), and quality by review (Q8, Q9, and Q10) to address future needs. It is a novel approach to creating and evaluating high-quality pharmaceutical products. Today, developing and analyzing pharmaceutical products with quality features is an essential part of the modern approach.

While it is a significant option for enhancing product quality, implementing it on an industrial scale proves challenging. Establishing a design space and control strategy is fundamental to the quality by design approach. while ensuring repeatability and accuracy. Various mathematical models are employed to analyze mathematical data and generate a design space. (Patil AS, Pethe AM. (2013)

Quality is of paramount importance in the pharmaceutical industry. Instead of merely testing the final product, Quality by Design (QbD) is a modern approach that integrates quality into both the product and the process from the very start. (Vogt FG, Kord AS.(2011)

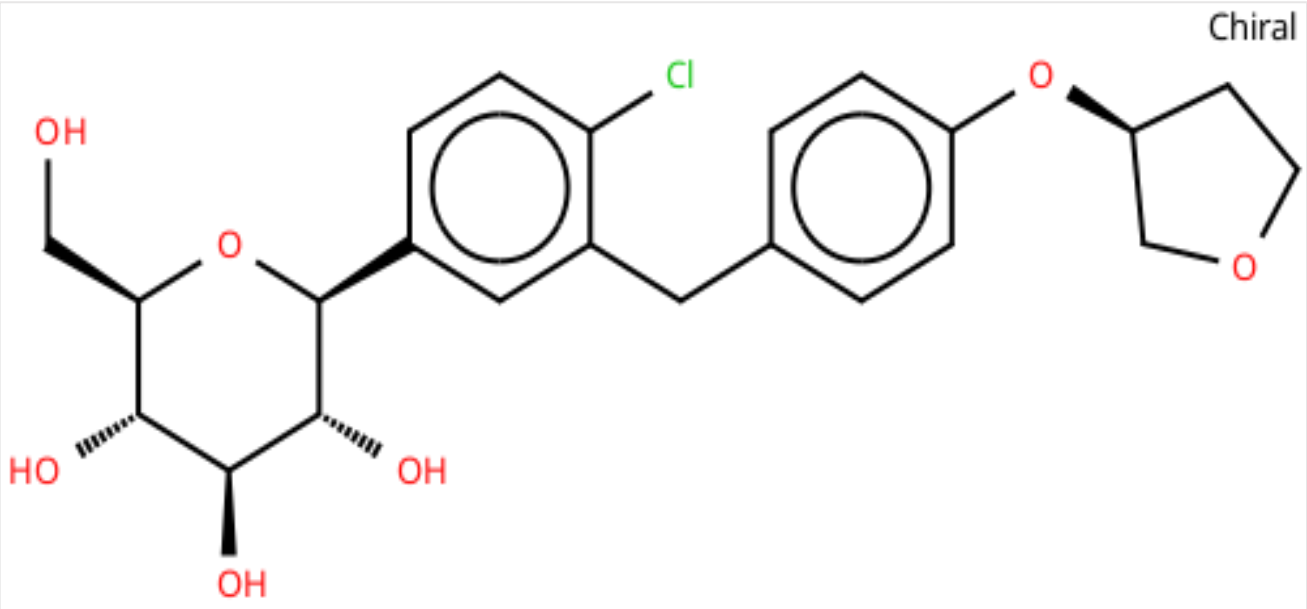
Drug Profile

Drug	**Empagliflozin**
IUPAC formula	4-(1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy) benzyl] phenyl)
Chemical Formula	C23H27ClO7
Molecular Weight	450. 91 g/mol
Dosage Form	10 mg, 25mg (pale yellow, round, biconvex)
Administration Route	Oral
Partition coefficient (log P)	1.7
Dissociation constant	12.57
Melting Point	$151\text{-}153^{0c}$

Marketed Formulation

Approved by the FDA in 2014, it is available in four formulations: Jardiance (empagliflozin), Glyxambi (empagliflozin and linagliptin), Synjardy (empagliflozin and metformin), and Synjardy XR (empagliflozin and extended-release metformin).

Structure of Empagliflozin



Various analytical methods have been reported for the determination of Empagliflozin

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue IV April 2026

UV-Visible Spectroscopy

Sr. No	Title	Description	References
1.	Method Development and Validation of Empagliflozin in Bulk and Pharmaceutical Dosage Form using UV Spectroscopy	**Solvent**- Ethanol & Water **Wavelength**- 223nm **Linearity**- 1-30ug/ml **Robustness**- 0.20 **Ruggedness**- 0.03 **R^2**- 0.998	Shaik Bima Benazir, Jorige Archana (2021)

Qbd Based

Sr. No	Title	Description	References
1	The application of quality by design in the development of the liquid chromatography method to determine Empagliflozin in the presence of its organic impurities	**Solvent**- Acetonitrile:Water (72:28) %v/v **Stationary Phase**- column C18 (150*40 mm, 5 mm) Wavelength- 230nm	(Joanna Wittchckind Manoel, 2020).

RP-HPLC

Sr. No	Title	Description	References
1	RP-HPLC Method Development & Validation of Empagliflozin by using QbD Approach	**Solvent**- 0.05 M potassium dihydrogen orthophosphate buffer pH 3 and acetonitrile in a ratio of (40:60 v/v) **Stationary Phase**- C18 Segment **Wavelength**- 228nm **Detector**- PDA	Prerana Bhavsar, Subodh Gangurde (2025)
2	New validated RP-HPLC method for the estimation of empagliflozin in human plasma	**Stationary Phase**- C18 column (250 mm × 4.6 mm, 5 µm) **Solvent**- Methanol : acetonitrile, 50:50% v/v **Wavelength**- 270nm **Flow Rate**- 1.0 ml/min **R^2**- 0.999 **Detector**- PDA	N. Padmaja, T. Desalegn, (2018)

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3	Empagliflozin: RP-HPLC based analytical method development and validation	**Stationary Phase**- ODS Column **Solvent**- 0.1%trifluoroacetic acid solution:acetonitrile in a 70:30 (v/v) **Wavelength**- 224nm **Flow Rate**- 1.0 ml/min **Linearity**- 30ug/ml. **R^2**- 0.999 Detector- PDA	Yogeshwari Jambhulkar, Nitu Madan (2024)
4	Analytical method development and validation of emphagliflozin by rp-hplc	**Stationary Phase**- C18 column **Solvent**- methanol and 0.05% acetic acid (75:25) v/v, pH 3.3–3.5) **Wavelength**- 224nm **R^2**- 0.9995	
5	Development and Validation of an RP-HPLC Method for Determination of Empagliflozin in Empagliflozin Tablet	**Stationary Phase**- C18 (250 mm × 4.6 mm, 5 µm particle size) **Solvent**- 0.01 M NaH2PO4 (as buffer) and acetonitrile (60:40) %v/v **Detection**- 210nm **R^2**- 0.999	Dr. K M Khairul Alam, Tanbin Jahan Ferdousy (2023)
6	New analytical method development and validation of empagliflozin (anti-diabetic) drug by rp-hplc method in bulk and pharmaceutical dosage form	**Stationary Phase**- Agilent Eclipse plus C18 (250mm ×4.6, 5µm **Solvent**- Acetonitrile and Monopotassium phosphate buffer (45:55) %v/v **Wavelength**- 224nm **R^2**- 0.9987	Sarfaraj Ahamad Khan, Dr. Chandanam Sreedhar (2019)

UPLC

Sr. No	Title	Description	References
1	Development and Validation of UPLC Method for the Simultaneous Estimation of Saxagliptin and Dapagliflozin in Tablet Dosage Form	**Stationary Phase**- UPLC ethylene bridge (BEH) C18 1.7 m RP column **Solvent**- 0.1% OPA and CAN (40:60) %v/v **PDA Detection**- 254nm **Flow Rate**- 0.3ml/min	Madhavi, S., and A. P. Rani. (2017)

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HPTLC

Sr. No	Title	Description	References
1	Stability indicating HPTLC method development and validation for determination of empagliflozin in bulk drug and tablet dosage form	**Stationary Phase**- precoated with silica gel 60 F_{254} **Solvent**- Chloroform: Methanol: Glacial acetic acid (8.5: 1.5: 0.2, v/v/v) **Densitometric detection**- 225nm	Nutan B. Raut, Padmanabh B. Deshpande (2022)
2	A novel validated stability indicating method for quantification of Empagliflozin in bulk and marketed formulation by HPTLC applying experimental design approach	**Stationary phase:** Aluminum plate coated with silica gel. **Solvent:** Ammonium acetate (2%): Triethylamine : Isopropyl alcohol (4:1:5 %v/v/v) **Detection:** 237nm	Manojkumar Munde, Nilesh Kulkarni (2023)
3	Stability indicating assay method for estimation of Empagliflozin using HPTLC	**Stationary Phase**- silica gel 60 F_{254} **Solvent**- Chloroform, Toluene, Methyl alcohol, and Methanolic acid mixed in a proportion of (8:4:2:0.1% v/v/v/v) **Densitometric detection**- 225nm	Vineeta Khanvilkar, Gayatri Vinchurkar (2025)

LC-MS

Sr. No	Title	Description	References
1	Development and validation of empagliflozin in human plasma using nevirapine as internal standard by liquid chromatography-tandem mass spectrometry.	**Stationary Phase**- Phenomenex Synergi, 4µm,4.6×75mm **Solvent**- mixture of 5mM Ammonium Acetate buffer with 0.1% Formic Acid: Acetonitrile (50:50 v/v) $\mathbf{R^2}$- 0.999	Jagadeesh, M., & Kumar, (2022)
2	Derivatization Method as a Residual Solvent of Acetic Acid by GC-MS Method in Empagliflozin Drug Substance: Development and Evaluation	**Stationary Phase**- Column: Agilent Technologies, Elite 5-MS, 30mm X 0.25 mm, 1.0-micron **Solvent**- Diluent: Methanol Source energy: 70eV IR and ^{1}HNMR.	Sushil Kumar Singh, Amol S Gaikwad (2025)

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Analytical Method Validation

Analytical method validation is the process of demonstrating that analytical procedures are suitable for their intended use. (Prabh Simran Singh (2011) More specifically, analytical method validation involves generating documented proof that a specified method consistently yields accurate test results to assess a product against its defined specifications and quality attributes. The method must be validatable, transferable, robust, reliable, accurate, and precise to support daily activities within the Quality Control environment. The method should not proceed to the validation phase until it is fully developed. Validation experiments must be conducted and documented using qualified and calibrated instrumentation and equipment. (Ravisankar P (2014)

The primary aim of any pharmaceutical manufacturing unit is to consistently produce medicines of the required quality at the most economical cost (Shushila DC, Deepa MD (2022) . The role of Validation is crucial, as it ensures reliable and repeatable outcomes for both routine analysis and stability testing. This has become increasingly important in the field of quality control and accreditation, particularly with the growing focus on dissolution, testing and impurity profiling in recent years (Nilam B, Vijaya B (2024).

As defined by the U.S. Food and Drug Administration (FDA), validation refers to a process of production and process control intended to confirm that drug products consistently maintain their identity, strength, quality, and purity. FDA guidelines issued in May 1987, a validation dossier must contain all the necessary data and testing procedures that demonstrate the system and process comply with established requirements (Jaha SM (2017).

The primary purpose of method validation is to demonstrate that an analytical method performs as intended, giving results that are accurate, reliable, and consistent. Validation of analytical methods is carried out in line with the International Council for Harmonization (ICH) guidelines, specifically ICH Q2 (Indian Pharmacopoeia (IP), (2022)

Type of validation and its purpose. (Toomula N, Kumar A, Kumar SD, Bheemidi VS. (2011)

Type of validation	**Purpose/when required**
New analytical procedure	For a newly developed method
Verification of compendial procedure	Confirm suitability of pharmacopeial methods
Method transfer	When method is transferred to another laboratory
Post-change validation	Significant changes to an existing method
Ongoing performance verification	To confirm continue suitability.

Parameters of Method Validation

Parameter	**Description (ICH)**	**Evaluation Method**	**Acceptance criteria of HPLC**
Specificity	Ability to measure analyte in presence of impurities	Blank, placebo, degraded samples	No interferance
Accuracy	Nearest true value	%RSD (intra/inter-day)	% Recovery- 98-102% % RSD of recovery concentration must be < 2
Precision	Degree of repeatability	Recovery studies (3 levels, triplicate)	RSD<2%
Linearity	Proportional response vs concentration	Calibration curve ($r^2 \geq 0.999$)	Coefficient correlation – NLT 0.999
LOD	Lowest detectable amount	$3.3 \times \sigma/S$	S/N > 2 or 3
LOQ	Lowest quantifiable amount	$10 \times \sigma/S$	S/N > 10
Range	Working concentration interval	Based on linearity, accuracy	-
Robustness	Resistance to small	Change pH, flow rate,	RSD < 2%

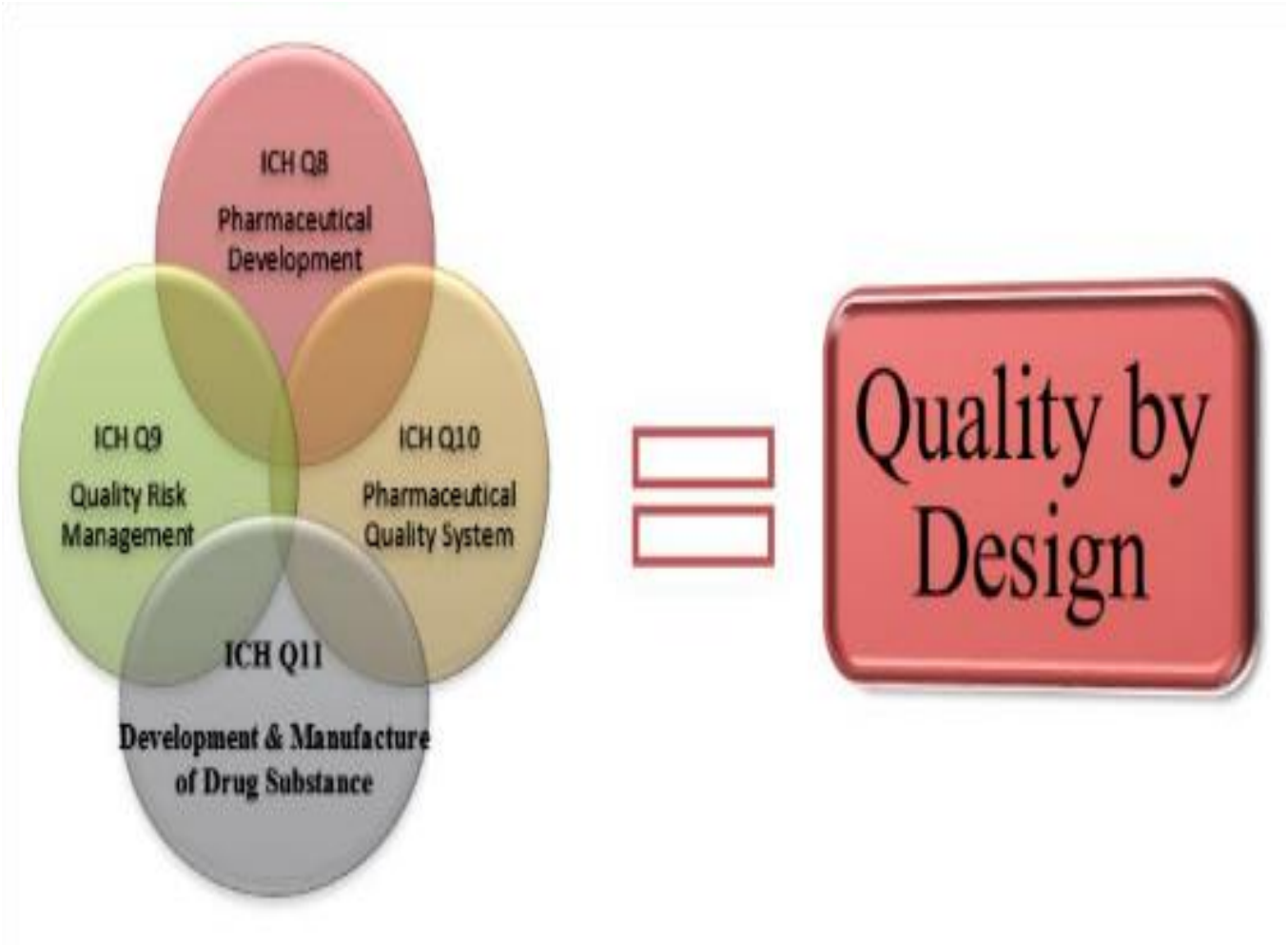
ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XIII Issue IV April 2026

	variations	temperature	
Ruggedness	-	-	Should meet all system suitability parameter

Quality By Design (Kadam VR, Patil M, (2017)

The USFDA has published specific QbD guidelines for immediate and extended-release drug products and biotechnology products. (Fukuda IM, Pinto CFF, (2018) Regulatory authorities continue to recommend the implementation of ICH quality guidelines such as Q8, Q9, Q10 and Q11. The concept of "Quality by Design" (QbD) was proposed as an approach that encompasses a better scientific understanding of critical processes and product quality, the design of controls and tests based on Scientific limitations of understanding in the field of development and use. (Beg S, Hasnain MS, (2019)

ICH guidelines Q8, Q9 and Q10 related to drug development, quality risk management and quality system structure by QbD.



Benefits of QbD (Waterman KC. (2011).

- QbD helps to improve the quality of the product and easy understanding of the process..
- To develop the quality of products.
- Good development decisions.

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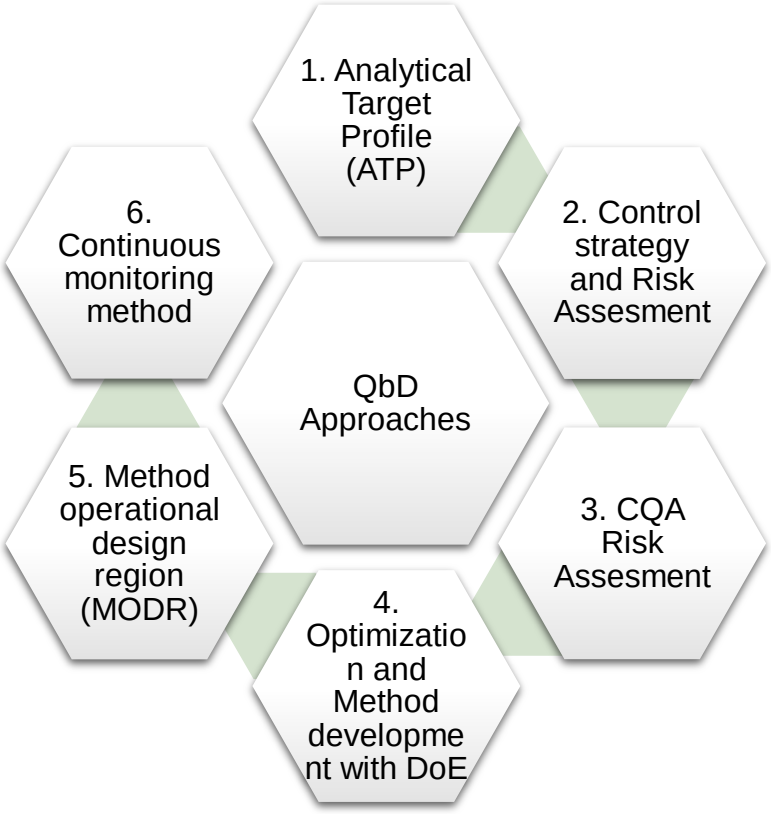
Qbd Approaches to Analytical Method Validation



CONCLUSION

This review examines various analytical methods developed for estimating empagliflozin. Analytical methods utilizing RP-HPLC and QbD is a well-established approach that yields more accurate and appropriate results. Future studies should prioritize the development of analytical methods that are both environmentally sustainable and cost-efficient without compromising their high performance.

Future Aspect

Future research on Empagliflozin Method Development hyphenated techniques such as GC–MS/MS and LC–MS/MS provide superior sensitivity and selectivity, enabling detection of analytes at trace and ultra-trace levels, which is essential for impurity profiling and degradation studies and UPLC is expected to significantly advance analytical method development and validation due to its superior speed, resolution, and sensitivity compared to conventional HPLC.

Significantly enhance detection sensitivity and reduce analysis time then bioanalytical development also can be done.

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