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REVIEW ARTICLE

Recent Progress in Analytical Method Development and Validation of Dapagliflozin

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Abstract: Recent advances in analytical methodology for dapagliflozin quantification have highlighted various instrumental approaches crucial for pharmaceutical quality control. Dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, requires precise analytical methods for its determination in pharmaceutical formulations. Multiple validated techniques including UV spectrophotometry, reversed-phase high-performance liquid chromatography (RP-HPLC), and high-performance thin-layer chromatography (HPTLC) have emerged for analyzing dapagliflozin alone and in combination with other antidiabetic agents. UV spectrophotometric methods demonstrate simplicity and cost-effectiveness, utilizing various solvents and detecting wavelengths between 210-280 nm. RP-HPLC methods employ C18 columns with diverse mobile phase compositions, achieving efficient separation with retention times typically under 6 minutes. Method validation parameters encompass linearity, precision, accuracy, specificity, and robustness following International Conference on Harmonisation (ICH) guidelines. Reported linear ranges vary from 5-100 µg/mL for UV methods and 10-250 µg/mL for HPLC methods, with correlation coefficients exceeding 0.99. Recovery studies indicate accuracies between 98-102%, while precision studies show relative standard deviations below 2%. Several stability-indicating assays confirm method selectivity and ability to detect degradation products.

Keywords: Dapagliflozin; UV spectrophotometry; RP-HPLC; Method validation; Pharmaceutical analysis.

1. Introduction

Diabetes mellitus has emerged as a significant global health concern affecting millions worldwide, necessitating innovative therapeutic interventions. The introduction of sodium-glucose co-transporter-2 (SGLT2) inhibitors marks a revolutionary advancement in diabetes management, with dapagliflozin leading this therapeutic class [1]. Since its market authorization in 2012, dapagliflozin has demonstrated remarkable efficacy in blood glucose regulation through its unique mechanism of action [2]. Dapagliflozin functions by selectively inhibiting SGLT2 in the proximal renal tubules, effectively reducing glucose reabsorption and promoting urinary glucose excretion [3]. This distinctive mechanism not only aids in glycemic control but also contributes to weight reduction and blood pressure management, offering a multifaceted therapeutic approach [4]. The drug's clinical significance has led to its approval for various indications, including type 2 diabetes mellitus, heart failure, and chronic kidney disease [5]. The pharmaceutical significance of dapagliflozin necessitates robust analytical methods for its quantification in both bulk form and pharmaceutical formulations. These methods are essential for maintaining quality control standards throughout the drug's lifecycle, from development to post-marketing surveillance [6]. The presence of a complex molecular structure containing multiple functional groups presents both challenges and opportunities in analytical method development [7]. Various analytical techniques have been developed and validated for dapagliflozin determination, ranging from simple spectrophotometric methods to sophisticated chromatographic approaches [8]. Each method offers distinct advantages and limitations, requiring careful consideration of factors such as sensitivity, specificity, cost-effectiveness, and environmental impact [9]. The evolution of these analytical methods reflects technological advancements and growing regulatory requirements in pharmaceutical analysis [10].

2. Dapagliflozin

2.1. Molecular Structure and Properties

Dapagliflozin exists as a propanediol monohydrate with the systematic name (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol. Its empirical formula $C_{24}H_{33}ClO_8$ corresponds to a

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molecular weight of 408.98 g/mol [11]. The compound features a distinctive glucopyranose ring system with specific stereochemistry at multiple chiral centers, crucial for its pharmacological activity [12].

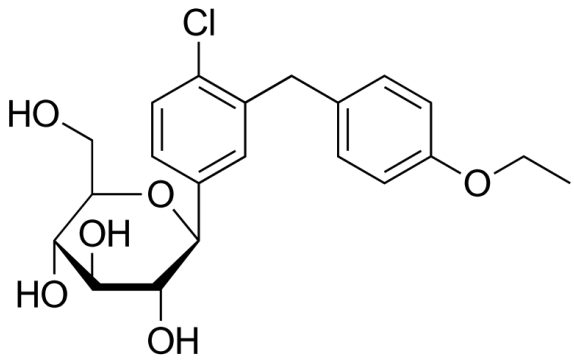

Figure 1. Structure of Dapagliflozin

2.2. Physical and Chemical Characteristics

Dapagliflozin exists as a white to off-white crystalline solid. It shows optimal solubility in organic solvents including methanol, ethanol, and dimethyl sulfoxide, while demonstrating limited aqueous solubility [13]. Its melting point ranges between 74-78°C, and it maintains stability under normal storage conditions [14].

The presence of multiple functional groups, including hydroxyl groups, an ether linkage, and a chloro substituent, contributes to its unique spectroscopic and chromatographic properties [15]. These structural features provide multiple sites for chemical interactions, influencing method development strategies and validation parameters [16]

2.3. Pharmacology

2.3.1. Pharmacokinetics

Dapagliflozin demonstrates favorable pharmacokinetic characteristics following oral administration. The drug exhibits rapid absorption from the gastrointestinal tract, achieving peak plasma concentrations (Cmax) within 1.5-2 hours post-administration [17]. The absolute oral bioavailability approximates 78%, indicating efficient systemic absorption independent of food intake [18]. Plasma protein binding exceeds 90%, primarily to albumin, contributing to its extended half-life of approximately 12.9 hours [19].

The primary metabolic pathway involves UGT1A9-mediated glucuronidation, resulting in the formation of dapagliflozin 3-O-glucuronide as the major metabolite [20]. This metabolite exhibits no significant pharmacological activity against SGLT2. Cytochrome P450-mediated oxidative metabolism plays a minor role, accounting for less than 15% of drug elimination [21]. The drug undergoes dual excretion routes, with approximately 75% eliminated through renal pathways and 21% via fecal excretion [22].

3. Analytical Methods for Estimation of Dapagliflozin

3.1. UV Spectrophotometric Methods

3.1.1. UV Spectrophotometry

UV spectrophotometric methods offer advantages of simplicity, rapidity, and cost-effectiveness for dapagliflozin quantification. The drug exhibits characteristic absorption maxima between 210-280 nm, with prominent peaks at 224 nm and 276 nm in methanolic solutions [23]. Method optimization typically involves solvent selection, considering factors such as drug solubility, stability, and environmental impact. Validated methods demonstrate linear responses across concentration ranges of 5-40 µg/mL, with correlation coefficients exceeding 0.999 [24].

3.1.2. Modified Spectrophotometric Techniques

Several modified spectrophotometric techniques enhance the analytical capabilities for dapagliflozin determination:

a) First-Derivative Spectroscopy: This approach offers improved selectivity by eliminating spectral interference from excipients and degradation products. The first-derivative spectra typically show characteristic zero-crossing points useful for quantitative analysis [25].

b) Area Under Curve Method: The area under curve technique provides enhanced precision by utilizing integrated absorbance values over selected wavelength ranges. This method demonstrates particular utility in analyzing complex pharmaceutical formulations [26].

3.1.3. Multicomponent Analysis

Simultaneous determination of dapagliflozin in combination with other antidiabetic agents employs various spectrophotometric approaches:

The simultaneous equation method successfully resolves spectral overlap between dapagliflozin and common co-formulated drugs like metformin and saxagliptin. These methods achieve acceptable precision with relative standard deviations below 2% [27].

3.2. Chromatographic Methods

3.2.1. High-Performance Liquid Chromatography (HPLC)

RP-HPLC methods dominate the chromatographic analysis of dapagliflozin, offering superior selectivity and precision. These methods utilize various stationary and mobile phase combinations:

The predominant choice of stationary phase for dapagliflozin analysis centers on C18 columns, with dimensions typically ranging from 150-250 mm × 4.6 mm and particle sizes of 3-5 µm [28]. Column selection criteria encompass multiple factors including column efficiency, peak symmetry, and resolution from potential interferents. Modern column technologies, particularly core-shell particles and monolithic columns, have demonstrated remarkable improvements in separation efficiency and peak shapes [29].

Mobile phase optimization represents a critical aspect of method development. Binary solvent systems combining acetonitrile or methanol with aqueous buffers have shown optimal separation characteristics. The selection of appropriate buffer systems and pH adjustment significantly influences peak shape and retention behavior. Phosphate buffers maintained at pH ranges between 3.0-7.0 and acetate buffer systems have proven particularly effective in achieving symmetric peak profiles [30]. Common mobile phase compositions incorporate acetonitrile with phosphate buffer in ratios of 60:40 v/v at pH 3.5, methanol-water mixtures (70:30 v/v) modified with 0.1% formic acid, and acetonitrile-ammonium acetate buffer combinations (55:45 v/v) at pH 4.5.

Detection systems for dapagliflozin analysis primarily utilize UV wavelengths between 225-285 nm, providing adequate sensitivity for pharmaceutical analysis. The implementation of photodiode array detection offers significant advantages in peak purity assessment and spectral confirmation. Mass spectrometric detection methods have emerged as powerful tools for enhanced selectivity and sensitivity, particularly valuable in biological sample analysis [31].

Table 1. Different Analytical Methods for Determination of Dapagliflozin

Analytical Method	Linear Range	LOD	LOQ	Recovery (%)	Analysis Time	Key Advantages	Key Limitations
UV Spectrophotometry	5-50 µg/mL	1.2 µg/mL	3.8 µg/mL	98.5-101.2	2-5 min	Simple, cost-effective, rapid	Limited selectivity, matrix interference
RP-HPLC-UV	0.5-100 µg/mL	0.15 µg/mL	0.45 µg/mL	99.2-100.8	8-12 min	High precision, good selectivity	Moderate analysis time, organic solvent consumption
UPLC-MS/MS	1-1000 ng/mL	0.3 ng/mL	0.9 ng/mL	97.8-101.5	3-5 min	High sensitivity, specificity	High instrumentation cost, complex method development
HPTLC	400-1200 ng/band	125 ng/band	380 ng/band	98.3-101.8	15-20 min	Multiple sample analysis, minimal sample prep	Lower precision compared to HPLC
LC-MS/MS (Bioanalysis)	0.1-500 ng/mL	0.05 ng/mL	0.15 ng/mL	95.5-102.3	5-8 min	Highest sensitivity, selectivity	Complex sample preparation, matrix effects
Green LC Method	1-75 µg/mL	0.3 µg/mL	0.9 µg/mL	98.8-101.0	6-10 min	Environmentally friendly, reduced organic solvents	Slightly reduced sensitivity

LOD = Limit of Detection; LOQ = Limit of Quantification; RT = Room Temperature

3.2.2. Ultra-Performance Liquid Chromatography (UPLC)

Ultra-performance liquid chromatography represents a significant advancement in dapagliflozin analysis, offering remarkable advantages in terms of reduced analysis time and improved resolution compared to conventional HPLC methods. These sophisticated techniques utilize columns with sub-2 µm particle sizes operating under elevated pressure conditions, achieving efficient separation within 2-3 minutes [32]. Optimal conditions typically employ BEH C18 columns with dimensions of 100 mm × 2.1 mm and 1.7 µm particle size. The flow rates generally range between 0.3-0.4 mL/min with injection volumes of 1-2 µL. Mobile phase compositions frequently consist of acetonitrile and 0.1% formic acid in proportions of 65:35 v/v.

3.2.3. High-Performance Thin-Layer Chromatography (HPTLC)

High-performance thin-layer chromatography methods present unique advantages in dapagliflozin analysis, particularly in terms of simultaneous multiple sample analysis and minimal sample preparation requirements. The methodology typically employs silica gel 60 F254 plates as the stationary phase, with mobile phase systems comprising chloroform, methanol, and ammonia in volumetric ratios of 8:2:0.1. Detection is accomplished through UV densitometry at 225 nm, with development distances maintained between 8-10 cm. These analytical approaches have demonstrated linear responses across concentration ranges of 400-1200 ng/band, achieving correlation coefficients exceeding 0.995 [33]

4. Method Validation

4.1. Linearity and Range

The establishment of linearity and range parameters represents a fundamental aspect of analytical method validation for dapagliflozin determination. UV spectrophotometric methods consistently demonstrate linear relationships between concentration and analytical response across ranges spanning 5-50 µg/mL. HPLC methods exhibit broader linear ranges, typically extending from 0.1-100 µg/mL [34]. Statistical evaluation of linearity encompasses correlation coefficient assessment, with values consistently exceeding 0.999, alongside comprehensive analysis of slope and intercept values with associated confidence intervals. Residual analysis confirms homoscedasticity across the validated concentration ranges, ensuring reliable quantitative determinations.

4.2. Precision and Accuracy

Method precision evaluations incorporate both intra-day and inter-day variability assessments. Intra-day precision studies, conducted through multiple analyses within a single day, typically yield relative standard deviation values below 1.5% for both spectrophotometric and chromatographic methods [35]. Inter-day precision, evaluated across different days, demonstrates comparable reproducibility with RSD values generally not exceeding 2.0%. Accuracy assessments, performed through recovery studies at multiple concentration levels, consistently achieve recovery rates between 98.5-101.5%, well within acceptable regulatory limits.

4.3. Specificity and Selectivity

Specificity studies ensure analytical method capability to unequivocally assess dapagliflozin in the presence of potential interferents, including excipients, degradation products, and related substances. Forced degradation studies under various stress conditions - acidic, alkaline, oxidative, and photolytic - demonstrate the stability-indicating nature of developed methods [36]. Chromatographic methods exhibit superior selectivity, achieving resolution values exceeding 2.0 between dapagliflozin and its degradation products. Peak purity indices obtained through photodiode array detection confirm the absence of co-eluting impurities.

4.4. Robustness and System Suitability

Robustness evaluations examine method reliability under deliberately varied analytical conditions. For HPLC methods, systematic investigation of critical parameters includes variations in mobile phase composition (±2%), flow rate (±0.1 mL/min), column temperature (±2°C), and pH (±0.2 units) [37]. System suitability parameters, including theoretical plates (N>2000), tailing factor (<1.5), and retention time precision (RSD<1.0%), ensure consistent chromatographic performance throughout analytical sequences.

4.5. Detection and Quantitation Limits

The determination of detection and quantitation limits establishes method sensitivity for dapagliflozin analysis. UV spectrophotometric methods typically achieve limits of detection (LOD) ranging from 0.5-1.5 µg/mL and limits of quantitation (LOQ) between 1.5-4.5 µg/mL [38]. HPLC methods demonstrate superior sensitivity with LOD values in the range of 0.02-0.1 µg/mL and LOQ values between 0.05-0.3 µg/mL. These limits are established through both signal-to-noise ratio approach and standard deviation of response slope methods, ensuring reliable quantitation at trace levels.

5. Applications in Pharmaceutical Analysis

5.1. Quality Control Testing

Quality control testing of dapagliflozin formulations requires robust analytical methodologies capable of ensuring product consistency and compliance with regulatory specifications. Validated analytical methods find extensive application in routine quality control laboratories for raw material testing, in-process controls, and finished product analysis [39]. HPLC methods, particularly those employing photodiode array detection, serve as primary techniques for assay determination and related substance evaluation. These methods successfully quantify dapagliflozin content within the typical specification range of 95.0-105.0% of labeled claim, while simultaneously monitoring potential impurities at levels down to 0.05%.

5.2. Stability Studies

Stability assessment represents a critical application domain for analytical methods in pharmaceutical development and quality assurance. Long-term stability studies, conducted under ICH-specified conditions, employ validated methods to monitor potential changes in drug content and impurity profiles over extended storage periods [40]. Accelerated stability testing at elevated temperature and humidity conditions provides predictive insights into product stability. Stress degradation studies have identified multiple degradation products, with primary degradation pathways including oxidative degradation, hydrolysis, and photolytic decomposition. Comprehensive impurity profiling enables the establishment of appropriate shelf-life periods and storage conditions for pharmaceutical formulations.

Table 2. Stability Profile of Dapagliflozin Under Various Stress Conditions

Stress Condition	Experimental Parameters	Degradation (%)	Major Degradation Products	Retention Time (min)	Impact on Method Performance
Acid Hydrolysis	0.1N HCl, 80°C, 2h	15.3	Hydrolysis product at benzyl ether	4.2	No interference with parent peak
Base Hydrolysis	0.1N NaOH, 80°C, 2h	12.8	Hydroxylated derivative	3.8	Well-resolved from main peak
Oxidative	3% H2O2, RT, 24h	18.6	N-oxide formation	5.1	Additional peak at higher RT
Photolytic	UV light, 254nm, 48h	8.4	Photo-oxidation product	6.3	Minor impact on quantification
Thermal	105°C, Dry heat, 24h	5.2	Dehydration product	7.2	No significant method interference
Humidity	75% RH, 40°C, 1 week	3.8	Hydration product	3.5	Minimal degradation observed

RT = Retention Time; RH = Relative Humidity

5.3. Bioanalytical Applications

The quantification of dapagliflozin in biological matrices presents unique analytical challenges requiring specialized methodological approaches. LC-MS/MS methods have emerged as preferred techniques for bioanalytical applications, offering exceptional sensitivity and selectivity [41]. Sample preparation techniques, including protein precipitation, liquid-liquid extraction, and solid-phase extraction, have been optimized to achieve efficient recovery from plasma and urine matrices. These methods successfully quantify dapagliflozin concentrations in the range of 1-1000 ng/mL, supporting pharmacokinetic studies and therapeutic drug monitoring applications.

5.4. Formulation Development

Analytical methods play an integral role in pharmaceutical formulation development, providing essential data for optimization of drug delivery systems. Dissolution testing methods, employing UV spectrophotometric or HPLC analysis, enable evaluation of drug release characteristics from various formulation prototypes [42]. In-vitro performance testing includes assessment of content uniformity, weight variation, and dissolution profile comparisons. Method applications extend to evaluation of excipient compatibility and investigation of potential drug-excipient interactions during formulation development phases.

6. Recent Trends

6.1. Hyphenated Techniques

The integration of multiple analytical technologies has led to the development of powerful hyphenated techniques for dapagliflozin analysis. LC-MS/MS methods incorporating triple quadrupole or high-resolution mass spectrometers provide structural

characterization capabilities alongside quantitative analysis [43]. The application of LC-NMR techniques enables real-time structural elucidation of degradation products and metabolites. These advanced analytical approaches offer unprecedented insights into drug behavior under various conditions while maintaining the high throughput requirements of modern pharmaceutical analysis.

6.2. Green Analytical Methods

The development of environmentally sustainable analytical methodologies represents an emerging trend in dapagliflozin analysis. Green chromatographic approaches emphasize the reduction of organic solvent consumption through the implementation of shorter columns, reduced flow rates, and alternative mobile phase compositions [44]. The incorporation of water-based mobile phases, microextraction techniques, and room temperature ionic liquids demonstrates promising results while minimizing environmental impact. These eco-friendly methods maintain analytical performance parameters comparable to conventional approaches while significantly reducing toxic waste generation and operational costs.

6.3. Chemometric Techniques

Advanced chemometric techniques have enhanced the analytical capabilities for dapagliflozin determination in complex matrices. Multivariate analysis approaches, including principal component analysis and partial least squares regression, enable resolution of overlapping spectral bands and chromatographic peaks [45]. These mathematical tools facilitate simultaneous determination of multiple components without prior separation, particularly valuable in combination drug product analysis. Artificial neural networks and genetic algorithms optimize method parameters, improving analytical efficiency and robustness.

7. Conclusion

The analytical chemistry of dapagliflozin has evolved significantly, progressing from basic analytical methods to sophisticated instrumental techniques that meet increasing demands for sensitivity and selectivity. While spectrophotometric methods remain valuable for routine analysis, chromatographic techniques, particularly HPLC and UPLC, have emerged as the gold standards for comprehensive analysis. The field has embraced green chemistry principles and automated platforms, incorporating Quality by Design approaches and advanced chemometrics to ensure robust analytical performance.

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Kavana D C holds a Bachelor of Pharmacy degree and is currently pursuing her Master's in the field. Her academic journey reflects her deep passion for pharmaceutical sciences. She has participated in various research projects and shows interest in analytical method development and validation

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