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REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF DAPAGLIFLOZIN AND METFORMIN HCL IN PURE AND PHARMACEUTICAL DOSAGE FORM

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ABSTARCT
Dapagliflozin, one of the earliest sodium-glucose transporter 2 (SGLT2) inhibitors, plays a significant role in managing type 2 diabetes mellitus (T2DM), chronic kidney disease, and heart failure. Metformin, a first-line treatment for T2DM, exerts its effects by suppressing hepatic gluconeogenesis and counteracting glucagon activity. Dapagliflozin received FDA approval on January 8, 2014, and later, on June 12, 2024, the FDA authorized AstraZeneca's XIGDUO XR (a dapagliflozin/metformin combination) for improved glycemic control in children aged 10 years and older with T2DM. This combination therapy, complemented by a healthy diet, also aids in managing elevated levels of triglycerides and cholesterol. A comprehensive review of analytical methods used for the quantification of dapagliflozin, metformin, and their combination in bulk drugs, pharmaceutical formulations, and biological samples is presented. Techniques explored in major pharmaceutical and analytical journals include spectrophotometric methods, chromatographic methods such as HPLC, RP-HPLC, and HPTLC, as well as liquid chromatography-tandem mass spectrometry (LC-MS/MS).

KEYWORDS: Dapagliflozin, Metformin, Gluconeogenesis, HPLC, UV.

INTRODUCTION[1-3]

Dapagliflozin, a pioneering sodium-glucose cotransporter 2 (SGLT2) inhibitor, is administered as a single daily dose to effectively reduce hepatic gluconeogenesis and modulate the actions of glucagon. This compound, chemically identified as (2S,3R,4R,5S,6R)-2-[4-chlorophenyl-3-(4-ethoxyphenyl) methyl-propane-1,2-diol; hydrate; -6-(hydroxymethyl) oxane-3,4,5-triol, requires hepatic activation to exert its therapeutic effects. Dapagliflozin targets the SGLT2 enzyme in the proximal convoluted tubule of the kidney, thereby inhibiting glucose reabsorption and promoting glycosuria, which is essential for reducing glucose levels and addressing gluconeogenesis. Metformin remains the cornerstone therapy for managing type 2 diabetes mellitus (T2DM). This medication functions by suppressing hepatic gluconeogenesis after hepatic activation of its parent compound. Initially studied in the 1950s, the structural formula of metformin, 3-(diaminomethylidene)-1,1-dimethylguanidine, facilitates its role as an adjunct to a balanced diet for effectively lowering blood glucose levels.

Physical and Chemical properties[4-7]

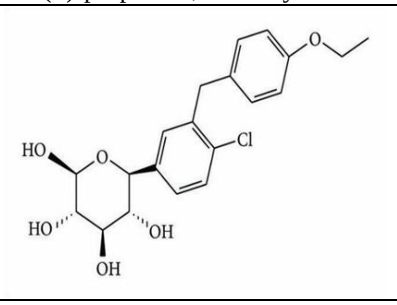
- Dapagliflozin is a non-hygroscopic, non-ionizable compound that appears as a white to off-white crystalline powder. Its IUPAC name is (2S,3R,4R,5S,6R)-2-[4-chlorophenyl]-3-[(4-ethoxyphenyl)methyl]-6-oxane(hydroxymethyl)-3,4,5-triol, and its molecular formula is C21H25ClO6. The molecular weight of dapagliflozin is 408.9 g/mol, and its melting point ranges between 55°C and 60°C.
- Metformin hydrochloride, on the other hand, is a white to off-white crystalline powder with a bitter taste. Its IUPAC name is 3-(diaminomethylidene)-1,1-dimethylguanidine hydrochloride, and the molecular formula is C4H11N5. It has a molecular weight of 165.63 g/mol and a melting point of 219°C to 226°C. Metformin hydrochloride is freely soluble in water and 95% alcohol but exhibits poor solubility in organic solvents such as acetone, ether, and chloroform.

Analytical Method Development[15-21]

Analytical method development and validation are pivotal processes in the realm of drug discovery, development, and pharmaceutical manufacturing. These

steps ensure the accurate assessment of a drug substance's purity and potential toxicity. The development phase involves selecting an appropriate and precise assay procedure to evaluate the composition of a pharmaceutical formulation. Furthermore, it ensures that the selected method is suitable for analyzing the concentration of samples consistently within a laboratory setting. Adherence to established protocols and acceptance criteria, as detailed in the ICH Q2(R1) guidelines, is critical during this process. Both method development and validation are integral to every stage of pharmaceutical production, from initial research to final product manufacturing. Despite their significance, the literature reveals an absence of a specific analytical method tailored exclusively for the combination of dapagliflozin and metformin hydrochloride. However, several methodologies, including UV spectrophotometry, reverse-phase high-performance liquid chromatography (RP-HPLC), high-performance thin-layer chromatography (HPTLC), stability-indicating RP-HPLC, and ultra-fast liquid chromatography (UFLC), have been documented for analyzing these compounds in combination with other drugs.

Drug profile[10-14]

	Dapagliflozin	**Metformin hydrochloride**
CAS number	461432-26-8	1115-70-4
Molecular formula	C21H25ClO6	C4H11N5 • HCl
Drug category	sodium-glucose co-transporter 2 (SGLT2) inhibitors	Biguanides
Chemical name	2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol compound with (S)-propane-1,2-diol hydrate	1,1-Dimethylbiguanide hydrochloride
Structure		
Characteristics	white to off-white, crystalline powder	white to off-white crystalline powder with a bitter taste
Solubility	soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide	highly soluble in water pH 9.5 phosphate buffers
Molecular weight	408.873 g/mol	129.164 g/mol
Melting point	55-60 °C	222-226ºC
Boiling point	609°C at 760 mmHg	224.1°C at 760 mmHg
Protien binding	91%	negligible plasma protein binding
Elimination half life	12.9 hours	6.2 hours
Pka	12.6	12.4
Log p	2.27–2.65	1.43.
Maximum concentration	224 nm	230 nm
Uses	type 2 diabetes	high blood sugar

Mechanism of action of dapagliflozin[19,20,21,24,27,29,30,31,32,33]

Dapagliflozin inhibits the sodium-glucose co-transporter 2 (SGLT2), which is primarily found in the proximal tubule of the nephron. SGLT2 is responsible for reabsorbing about 90% of glucose from the kidneys back into the bloodstream. By blocking this transporter, dapagliflozin promotes the excretion of glucose in the urine. This process helps improve blood sugar control and may also contribute to weight loss in patients with type 2 diabetes mellitus.

Mechanism of action of metformin Hcl[18,23,25,28,34]

Metformin differs significantly from other oral diabetes medications. It works by reducing liver glucose production, limiting glucose absorption in the intestines, and enhancing insulin sensitivity. This results in improved glucose uptake and utilization in the body. Research confirms that metformin's effectiveness in managing type 2 diabetes and regulating blood sugar levels is largely due to its inhibition of mitochondrial complex I activity.

Literature Review

Sr. No.	Title/ Method	Descriptions	Ref. No.
1.	Development and validation of QBD–assisted RP- HPLC method for Dapagliflozin and metformin HCL in bulk and it's combined dosage forms	Column :250 ×4.6mm, 5µm Mobilephase:65%; Acetonitrile :35%KH2PO4 Flow Rate : 1 ml /min Wave length: 227 Retention time: 2.48mins	[34]
2.	Stability indicating HPLC method development and validation for simultaneous estimation of metformin HCL and Dapagliflozin in API and pharmaceutical dosage form	Column :4.6mm × 250mm :5µm Mobilephase:65%, Acetonitrile : 35%water Flow Rate : 1ml/min Wave length : 240nm Retention time : 2.13 and 5.41mins	[35]
3.	Application of dose in developing a validated RP-HPLC method to evaluate Dapagliflozin and metformin combined tablet dosage form	Mobilephase:40%,Acetonitrile:40%, menthol:20% Flow Rate : 1.0 ml/min Wave length:215nm Retention time :2.17 and 3.15	[36]
4.	Stability indicating HPLC method development and validation for simultaneous estimation of Dapagliflozin and metformin tablet dosage form	Column : C18 (4.6×250)5µm Mobilephase:75%Methanol, Acetonitrile :25%water Flow Rate : 1ml/min Wave length : 233nm Retention time : 5.099 and 2.165 min	[37]
5.	Development and validation of RP- HPLC method for simultaneous estimation of Dapagliflozin and Metformin in bulk and in synthetic mixture.	Column : Phenomonex C18(4.6mm×250mm,5µm) Mobile phase : 75% Acetonitrile :25%water Flow Rate :1ml/min Wave length : 285nm Retention time :3.2 and 5.4min	[38]
6.	Development of Validated Stability Indicating Assay Method for Simultaneous Estimation of Metformin and Dapagliflozin by RP- HPLC	Column :4.6×150nm,5µm Mobile phase : 70%, Acetonitrile:30%Acid buffer Flow Rate :1.0ml/min Wave length :260nm Retention time :2.097min and 3.691min	[39]
7.	A validated stability indicating HPLC method for simultaneous determination of metformin HCL and Dapagliflozin in bulk drug and tablet dosage form	Column:hypersilBDSC18 (250nm×4.6nm,5µm) Mobile phase : 50% Acetonitrile:50%buffer Flow Rate :1ml/min Wave length :240nm Retention time :2.791and 3.781mins.	[40]
8.	RP-HPLC Method for Dapagliflozin and Metformin HCL in Bulk and Combined Formulation	Column : Phenomonex C18(250nm×4.6nm) Stationary phase : 50% water, menthol:50% Flow Rate :1.0mlmin Wave length :230nm Retention time :2.178mins and 3.338min	[41]
9.	An improvement validated RP-HPLC method for simultaneous estimation of Metformin and Dapagliflozin from finish dosage form.	Column : Zorobax Eclipse plus phenyl hexyl C18(250mm×4.6mm,5µ) Mobile phase : 40% buffer :35% Menthol :25% Acetonitrile Flow Rate :1.0ml/min Wave length :267nm Retention time :2.63and9.34min	[42]
10.	Stability indicating RP- HPLC method development and validation for simultaneous estimation of Dapagliflozin propane diol monohydrate and Vildagliptin in tablet dosage form.	Column :Agilent Eclipse XDB (150mm×4.5nm,5 µ) Mobile phase : Gradient program dihydrogen phosphate buffer 50%: Acetonitrile :50% Flow Rate :1 ml/min Wave length :210 Retention time:9.11 and 2.58min	[26]
11.	Method development and validation for metformin HCL and Dapagliflozin by using RP-HPLC	Column : 250 mm × 4.6 mm, 5µ m Mobile phase : 45% buffer Acetonitrile:55% Flow Rate :1.0ml/min Wave length :220nm Retention time : 2-8 minutes	[43]

12.	A new RP-HPLC method development and validation for Dapagliflozin in bulk and tablet dosage form.	Column : 25 cm×4.6mm,5 µ m Mobile phase : 60% buffer, 40%Acetonitrile Flow Rate :1.0ml/min Wave length :237nm Retention time :3.461mins	[17]
13.	A Validated LC-MS/MS Method for Simultaneous Estimation of Dapagliflozin and Metformin in Pharmaceutical Dosage Form	Column : 2.1×100nm,2.7 µ m Mobile phase : 20% Acetonitrile 80%Water Flow Rate :0.2ml/min Retention time:15 min	[44]
14.	Development and stability indicating HPLC method for Dapagliflozin in API and pharmaceutical dosage form	Column:AgilentC18(4.6ml×150,5 µ m) Mobile phase : 40%,Acetonitrile :60% Flow Rate :1ml/min Wave length :222nm Retention time:3.160 and 3.067 min	[45]
15.	Chromatographic simultaneous quantification of dapagliflozin and metformin HCL in presence of the degradation products	Column: HYPERSILC18(150×4.6mm,5 µ m) Stationary phase : 5%, Acetonitrile:4%,methanol: 1% Flow Rate :0.5ml/min Wave length :236nm Retention time:8.314 and0,05 min	[46]
16.	Development and Validation of the Stability indicating Assay Methodology Employing LC-MS/MS for Concurrent Quantification of Dapagliflozin Propane diol Monohydrate and Metformin Hydrochloride: Probable degradants based on Mass Spectra	Column:C18(150×4.62mm,5 µ m Mobile phase : 30%, Acetonitrile:5%,methanol :65% Flow Rate :0.4ml/min Wave length :227nm Retention time:7.297 and 3.230 min	[47]
17.	Simple quantified and validated stability indicating stress degradation studies of oral anti- diabetic agent Dapagliflozin by RP –HPLC method	Column:C18(250×4.6mm,5 µ m) Mobile phase : 55% buffer, Acetonitrile:40%,methanol: 05% Flow Rate : 1ml/min Wave length :225nm Retention time:2.12 and0.05 min	[48]
18.	Implementation of QBD Approach to the Analytical Method Development and Validation for the Estimation of Metformin Hydrochloride in Tablet Dosage Forms by HPLC	Column:(250×4.6mm,5 µ m) Mobile phase : 70% buffer, Acetonitrile:30%methanol Flow Rate : 1ml/min Wave length :235nm Retention time:10 min	[49]
19.	Simultaneous analysis of Dapagliflozin and its three related impurities by stability-indicating UPLC method and in vitro toxicity evaluation	Column:(50×3.0mm,1.8 µ m) Mobile phase : 70% buffer, Acetonitrile:30% water Flow Rate : 0.1ml/min Wave length:230nm	[50]
20.	Analytical method development and statistical validation of Dapagliflozin in tablet dosage form and bulk form	Column:C18(250×4.6mm) Mobile phase : 60% buffer,40%methanol Flow Rate : 1ml/min Wave length :224nm Retention time:1.467 min	[51]
21.	Development and Validation of Stability Indicating RP-HPLC Method for the Simultaneous Estimation of Dapagliflozin Propane diol and Metformin Hydrochloride in Tablet Dosage Form	Column:(250×4.60mm,5 µ m) Mobile phase : 30% buffer,65%methanol,05% Acetonitrile Flow Rate :0.8ml/min Wave length :227nm Retention time:5.988 and 4.661 min	[52]
22.	Stability-Indicating RP-HPLC Method Development for Simultaneous Determination and Estimation of Dapagliflozin in Raw and Tablet Formulation	Column:(150mm×4.6mm,5 µ m) Mobile phase:75%methanol,25% water Acetonitrile Flow Rate :1ml/min Wave length :230nm Retention time:3.1 min	[53]
23.	Analytical method development validation	Column:C18(250mm×4.6I.D,5µ)	

	and forced degradation of Dapagliflozin by RP-HPLC	Mobilephase:85%methanol, Acetonitrile: 15% water Flow Rate :0.9ml/min Wave length :224nm Retention time:2.226 min	[54]
24.	Estimation of Dapagliflozin in Pure and Marketed Formulation by Validated Reverse Phase-High Performance Liquid Chromatographic Method	Column:sunsilC18(150×4.5mm,5µ) Mobilephase:85%, Acetonitrile: 15% water Flow Rate :1.0ml/min Wave length :225nm Retention time:2.74 min	[55]
25.	Development and Validation of UV Spectroscopic First Derivative Method for Simultaneous Estimation of Dapagliflozin and Metformin Hydrochloride in Synthetic Mixture.	Concentration range:0.5-2.5 µ g/ml Correlation coefficient:0.984 and 25-125 µ g/ml Wave length:235 and 272nm	[56]

CONCLUSION

In conclusion, the analytical techniques highlighted in this review underscore the critical role of HPLC and spectrophotometry in routine and advanced assessments of Dapagliflozin and Metformin HCl. The selection of an appropriate method depends on the specific analytical requirements, such as sensitivity, matrix complexity, and regulatory standards. Future advancements in analytical technologies, including the integration of green chemistry principles, could further enhance the precision, reliability, and eco-friendliness of these methodologies, contributing to improved pharmaceutical quality assurance and patient safety.

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