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Review Article

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A REVIEW ON COMPARENSIVE ANALYSIS OF METFORMIN HCL AND DAPAGLIFLOZIN

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ABSTRACT

Diabetes mellitus is increasingly prevalent due to modern lifestyle factors such as dietary habits, medication use, traditions, and lifestyle changes. Effective management of type 2 diabetes often requires the use of combination drug therapies, as single drugs may not provide sufficient control. Metformin HCL, a biguanide antihyperglycemic agent, and dapagliflozin, a Sodium Glucose Co-Transporter 2 (SGLT2) inhibitor, represent a promising combination for the treatment of type 2 diabetes. This study presents a comprehensive analysis of metformin HCL and dapagliflozin, focusing on their mechanisms of action, drug profiles, and the efficacy of their combination therapy. Various analytical techniques, including Reverse Phase High-Performance Liquid Chromatography (RP-HPLC), High-Performance Liquid Chromatography (HPLC), Ultraviolet (UV) spectroscopy, and Liquid Chromatography-Mass Spectrometry (LC-MS), were employed to analyse the drugs in both bulk and pharmaceutical dosage forms. The findings highlight the enhanced efficacy of double combination therapy with metformin HCL and dapagliflozin in managing type 2 diabetes mellitus, and provide detailed insights into their analytical profiles.

KEYWORDS

- Metformin HCL
- Dapagliflozin
- RP-HPLC
- UV – spectroscopy

INTRODUCTION

Diabetes mellitus is a chronic, progressive, incompletely understood metabolic condition chiefly characterize by hyperglycemia.[1] Diabetes mellitus is a chronic and serious metabolic disorder affecting nearly 400 million patients worldwide. Diabetes mortality rate is set to reach 4.5 million people annually, and it increases the risk of cardio-, nephro, neuro, and retinopathy. Type 2 diabetes, the most common type, accounts for about 90% of diabetic cases.[2]

Dapagliflozin belongs to a new class of oral anti-diabetic drugs, called Sodium Glucose Co-Transporter 2 inhibitor. It is indicated for the management of Diabetes Mellitus type 2, and functions to improve glycemic control in adults when combined with diet and exercise.
Metformin is a biguanide antihyperglycemic agent used for treating non-insulin dependent diabetes mellitus. It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose uptake.[3]

Treatment with metformin acts to lower blood glucose levels primarily via effects on hepatic output of glucose (gluconeogenesis), glucose absorption from the intestine, and by improving insulin sensitivity in peripheral tissues.[4] A new combination dosage form of Metformin HCL and Dapagliflozin is indicated for the treatment and management of diabetes. Combination of Dapagliflozin and Metformin HCL is marketed as a Tablet (XIGDUEO XR) containing 5mg/500mg, 5mg/1000mg, 10mg/ 500mg, 10mg/1000m. and in Xigduo 5mg/850mg, 5mg/1000mg.[1]

PHYSICAL AND CHEMICAL PROPERTIES OF DRUGS

A. METFORMIN HYDROCHLORIDE

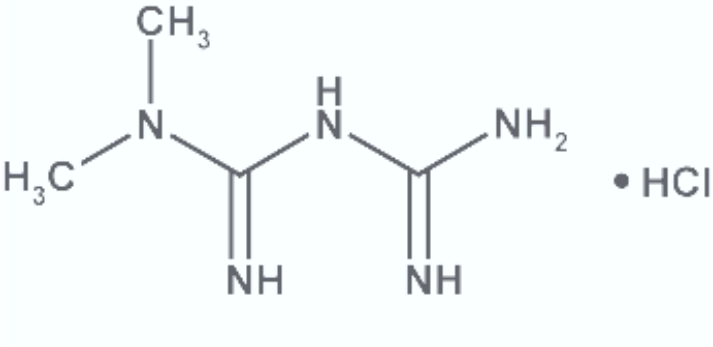

Figure-1: Structure of Metformin Hydrochloride.

1-Carbamimidamido-N, N-dimethyl methanimidamide hydrochloride, known for its IUPAC designation, is a potent oral anti-diabetic medication specifically designed for the management of type 2 diabetes mellitus. With a molecular formula of $C_4H_{12}ClN_5$ and a molar mass of 165.625 g/mol, this compound effectively helps in regulating blood glucose levels. It possesses a notable melting point range between 222-226ºC, which underscores its stability under moderate thermal conditions. The pKa value of 12.33 highlights its basicity, a characteristic crucial for its pharmacological efficacy. This drug exhibits excellent solubility in water, ethanol, and dimethyl formamide, facilitating its administration and absorption in various pharmaceutical formulations. As an essential therapeutic agent, it significantly contributes to improving the quality of life for patients with type 2 diabetes by aiding in the maintenance of optimal blood sugar levels.[5]

Mechanism of action

It is an oral anti-hyper glycemic agent (Type 2 diabetes) belongs to class of biguanides and useful for treating non-insulin-dependent diabetes mellitus. It decreases blood sugar levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization.[6] It is well established that metformin inhibits mitochondrial complex I activity, and it has since been postulated that its potent antidiabetic effects occur through this mechanism. The above processes lead to a decrease in blood glucose, managing type II diabetes and exerting positive effects on glycemic control.[5]

B. DAPAGLIFLOZIN

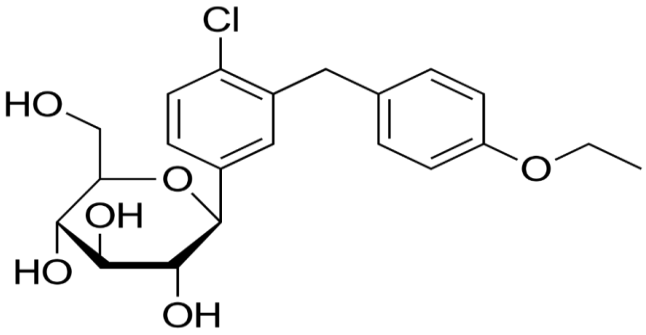

Figure-2: Structure of Dapagliflozin.

The compound, known by its IUPAC name as (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-6-(hydroxy methyl) oxane-3,4,5-triol, is a notable sodium-glucose co-transporter 2 (SGLT2) inhibitor used in the treatment of type 2 diabetes. This drug, with a molecular formula of $C_{21}H_{25}$ ClO_6 and a molar mass of 408.9 g/mol, plays a critical role in managing blood glucose levels by inhibiting the reabsorption of glucose in the kidneys, thereby promoting its excretion through urine. The compound's melting point is in the range of 55-58°C, indicating its physical stability under typical storage conditions. With a pKa value of 12.6, it is characterized by a relatively high acidity, which influences its solubility and absorption properties. The drug exhibits good solubility in solvents like ethanol and dimethyl formamide, facilitating its use in various pharmaceutical formulations. As an SGLT2 inhibitor, it provides a novel mechanism of action distinct from other antidiabetic agents, offering an effective therapeutic option for patients who require stringent blood sugar control. This pharmacological profile underscores its importance in the arsenal of treatments for type 2 diabetes, contributing to improved patient outcomes and quality of life.[7]

Mechanism of action

Dapagliflozin is inhibiting renal glucose reabsorption through the sodium- glucose co-transporter 2 offers an insulin-independent alternative to controlling blood glucose concentrations in patients with type 2 diabetes. Dapagliflozin is a first generation, selective SGLT inhibitor that blocks glucose transport with about 100-fold selective for SGLT2 over SGLT1. SGLT2 facilitates 90% of glucose reabsorption in the kidneys and so its inhibition allows for glucose to be excreted in the urine.[5]

Table 1: Integrated Analytical Methods for Simultaneous Determination of Dapagliflozin And Metformin Hcl In Bulk and Pharmaceutical Dosage Forms.

S.NO	TITLE/METHOD	METHOD DESCRIPTION	REF. NO	YEAR OF PUBLISHED
RP-HPLC Methods				
1.	RP-HPLC Method for Dapagliflozin and Metformin HCL in Bulk and Combined Formulation	**Colum:** Phenomenex C18 250mm x 4.6 mm, **Mobile phase:** Water: Methanol in the ratio of 50:50 **Flow rate:** s maintained at 5 1.0ml/min **Wave length of detection**: 230nm **Column temperature**: 30^0 C **Linearity:** 2-7 ppm for metformin HCL and 60-210 ppm for Dapagliflozin	[8]	December 2021
2.	Development and validation of QbD-assisted RP-HPLC method for dapagliflozin and metformin HCL in bulk and its combined dosage form	**Colum:** Intersil ODS column (250 x 4,6mm, 5 µm). **Mobile phase:** ACN: KH_2PO_4 (65:35%v/v) **Flow rate:** 1.0ml/min **Retention time:** 2.48 min **pH**: 4.5 **Resolution:** 12.65	[9]	February 2023
3.	Development and validation of RP-HPLC method for simultaneous estimation of dapagliflozin and metformin in bulk and in synthetic mixture	**Colum:** Phenomenex Luna C18 (4.6mm I.D. × 250mm, 5µm) **Mobile phase:** Acetonitrile: Water (75:25% v/v) **Flow rate:** 1mL/min. **Wavelength:** 285nm **Injection volume**:10 µl. **Retention time:** 3.2 for metformin and 5.4 for Dapagliflozin **Linearity:** 20–100µg/ml for metformin and 10–50µg/ml for Dapagliflozin	[10]	July 2017
4.	Stability indicating RP-HPLC method development and validation for estimation of dapagliflozin and metformin HCL.	**Colum:** Inertsil ODS C18 column (250mm x 4.6 mm, 5µ) **Mobile phase:** Potassium Dihydrogen ortho Phosphate buffer: Acetonitrile in the ratio of 50:50% v/v **Flow rate:** 1.0 ml/min **Wavelength:** 227 nm **Retention time**: 2.633 for Dapagliflozin and 5.620 for Metformin HCl **pH** :3.5, adjusted with 0.1% Orthophosphoric acid	[11]	August 2017
5.	An improved validated RP-HPLC method for the simultaneous estimation of metformin and dapagliflozin	**Column:** Unisol C18 (150 mm × 4.6 mm, 3 µ particle size) **Particle size** :3 µ **Mobile phase:** Methanol: Buffer **pH**: 3.5 **Flow rate:**0.8 ml/minute **Wavelength:** 245nm **Retention time:** 2.040 minutes and 3.733 minutes for DAP and MET hydrochloride, **Concentration range:** 20-120 µg/ml for MET (R2= 0.9988) and 10-60 µg/ml for DAP (R2= 0.9989)	[12]	March 2020
6.	Development of Validated Stability Indicating Assay Method for Simultaneous Estimation of Metformin and Dapagliflozin by RP- HPLC	**Colum:** Inspire (4.6 x 150mm, 5µm)5micro **Mobile phase:** Acetonitrile and 0.1M orthophosphoric acid buffer (70:30, v/v) **Flow rate:** 1.0mLmin **Wavelength:** 260nm **Detector:** Detector **Retention times:** MET and DAP were 2.097min and	[13]	January 2017

		3.691min **Concentration range**: 5-25µg/ mL for DAP and 500-2500µg/ mL for MET		
7.	Application of doe in developing a validated RP-HPLC method to evaluate dapagliflozin and metformin in combined tablet dosage form	**Mobile phase:** ACN: Menthol (40:40:20) %V/V **Flow rate:** 1.0ml/min **pH**:2.6 **Wavelength:** 280nm **Retention time:** 2.17 for Dapagliflozin and 3.15 for metformin	[14]	July 2023
8.	Chromatographic simultaneous quantification of dapagliflozin and metformin hydrochloride in presence of their degradation products	**Colum:** Hypersil TM ODS C18 column (150 x 4.6 mm, 5 µm) **Mobile phase:** 0.05 M potassium dihydrogen phosphate buffer (adjusted to pH 4.6 using orthophosphoric acid): acetonitrile: methanol (5:4:1, by volumes). **Flow rate:** 0.5mL/min **Wavelength:** UV detection at 236 nm. **Linearity:** 0.5 -20 µg/mL DAPA and 50 – 550 µg/mL MET	[15]	October 2017
HPLC METHOD				
9.	Stability indicating HPLC method development and validation for simultaneous estimation of dapagliflozin and metformin tablet dosage form	**Colum:** C18 column (4.6 × 250 mm) **Particle size**: 5 µm **Mobile phase:** Methanol: Water (75:25% v/v) **Flow rate:** 1.0 mL/min **Wavelength:** 233 nm **Retention time** 5.099 min FOR DAPA and 2.165 min for MET	[16]	July 2022
UV METHOD				
10.	Development and Validation of UV Spectroscopic First Derivative Method for Simultaneous Estimation of Dapagliflozin and Metformin Hydrochloride in Synthetic Mixture	**Wavelength:** 235nm for DAPA and 272nm for MET HCL **Quartz cells**: 1cm **Concentration range:** 0.5-2.5 µg/ml for MET HCL and 25-125 µg/ml for DAPA **Correlation coefficient**: 0.984 for Dapagliflozin and 0.982 for MET HCL	[17]	September 2015
11.	Development and validation of UV spectroscopic method for simultaneous estimation of Dapagliflozin and Metformin HCL in synthetic mixture	**INSTRUMENT:** double beam UV/Visible spectrophotometer **Wavelengths:** 225 nm for DAPA and 237 nm for MET HCL **quartz cells:** 10 mm **SOLVENT:** Methanol **Bandwidth:** 1 nm **wavelength accuracy**: ± 0.3 nm **Balance**: Shimadzu electronic analytical balance	[18]	March 2015
12.	A Novel Method Development and Validation of Dapagliflozin and Metformin Hydrochloride using Simultaneous Equation Method by UV– Visible Spectroscopy in Bulk and Combined Pharmaceutical Formulation including Forced Degradation Studies	**Wavelength:** 222 nm Dapagliflozin and 232 nm Metformin. **Linearity:** linearity ranges 2 – 32 µg/ml Dapagliflozin and 1 – 20µg/ml Metformin. **correlation coefficient values (R2):** 0.999 **LOD and LOQ:** Dapagliflozin was found to be 0.0241 µg/ml and 0.0293 µg/ml and Metformin 0.0732 µg/ml and 0.0890 µg/ml. **% RSD value:** 0.1845 % Dapagliflozin and 0.2052 % Metformin	[19]	2020
13.	Bioanalytical method development and validation of dapagliflozin and metformin hydrochloride in combined dosage form using uv spectroscopy	**Wavelength: dapagliflozin** 222 nm and metformin 232 nm. **Linearity:** Dapagliflozin2 – 32 µg/ml and Metformin 1 – 20µg/ml. **coefficient values (R2):** 0.999 **% RSD value:** Dapagliflozin 0.1845 % and Metformin 0.2052 %.	[20]	2020

		concentration level: 96.82 - 99.8 % for Dapagliflozin and 98.15 to 99.35 % for Metformin.		
14.	Spectrophotometric Absorption Correction Methods for the Estimation of Fixed-Dose Combinations of Dapagliflozin and Metformin Hydrochloride	**Wavelength:** 275nm (DAPA), and 245nm (MET) concentration ranges: dapagliflozin 2–10 µg/mL and metformin 20–100 µg/mL. **accuracy:** 100.25 + 0.0459% and 99.82 + 0.059. **RSD Value**: RSD 2% **Instrument**: UV-1800 SHIMADZU UV-spectrophotometer **Quarts**: 10 mm Quartz matched cells **Pathlength**: 1 cm	[21]	September 2023
15.	Analytical Spectrometric Study for Determining Dapagliflozin Propanediol Monohydrate Individually or In Presence of Metformin Hydrochloride in Tablets Formulation	**Instrument**: Spectro Scan 80 DV, UV/Vis spectrophotometer. **Linearity range:** dapagliflozin (2.61– 31.23) µg/mL and metformin (5.21 – 41.64) µg/mL. **Wavelength: dapagliflozin** 223.5 nm and metformin 233 nm. **correlation coefficients**: dapagliflozin R2 = 0.9989 and metformin hcl R 2 = 0.9994. **LOD and LOQ value**: dapagliflozin 0.569 µg/mL and 1.724 µg/mL, and metformin 0.732 µg/mL and 2.218 µg/mL.	[22]	2020
LC-MS/MS METHOD				
16.	A Validated LC-MS/MS Method for Simultaneous Estimation of Dapagliflozin and Metformin in Pharmaceutical Dosage Form63	**Colum:** Poroshell 120 EC-C18 (2.1×100 mm, 2.7 µm) **Mobile phase:** ammonium acetate: acetonitrile (20:80, v/v) **Flow Rate:** 0.2 ml/min **Concentration range:** 25-500 ng/mL for dapagliflozin and 100-2000 ng/mL for metformin **Column temperature:** 35°C **m/z:** dapagliflozin 426.20-107.20 and metformin 130.10-60.10.	[23]	December 2020

CONCLUSION

This review highlights the various analytical methods used for the quantification of dapagliflozin and metformin hydrochloride in pharmaceutical dosage forms. Key methods include RP-HPLC, HPLC, UV spectroscopy, and LC-MS/MS, each with distinct advantages. RP-HPLC is versatile and precise, making it suitable for analysing complex mixtures and conducting stability studies. UV spectroscopy offers a simple, cost-effective option for routine analysis, while LC-MS/MS provides high sensitivity and specificity, ideal for detecting low concentrations. Despite their strengths, these methods face challenges such as matrix effects and the need for rigorous validation. Future advancements aim to enhance the sensitivity, selectivity, and throughput of these analytical techniques. This review serves as a valuable resource for researchers and practitioners, aiding in the selection of appropriate analytical methods to improve the quality and efficacy of diabetes treatments.

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