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Review Article

A Review Article on Analytical Techniques for Simultaneous Estimation of Dapagliflozin & Linagliptin

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A B S T R A C T

Diabetes mellitus is a chronic metabolic disorder that necessitates combination therapy for optimal glycemic control. This review focuses on analytical techniques developed for the simultaneous estimation of these two agents in bulk and pharmaceutical formulations. Emphasis is placed on UV-spectrophotometric and high-performance liquid chromatography (HPLC) methods owing to their simplicity, accuracy, and cost-effectiveness. The UV-spectrophotometric method employs simultaneous equation techniques at 295 nm for dapagliflozin and 225 nm for linagliptin, exhibiting excellent linearity within 2–10 µg/mL concentration range. Multiple HPLC methods have been reported using C_{18} columns with varying mobile phases such as phosphate buffer–acetonitrile systems, achieving robust separation and reliable detection at wavelengths between 223–244 nm. All methods were validated according to ICH guidelines, assessing parameters like linearity, precision, accuracy, specificity, and robustness, with correlation coefficients (R^2) consistently >0.99, confirming high reliability. Additionally, stability-indicating methods were included to ensure detection of degradation products, supporting quality control applications. Overall, the reviewed analytical methods provide reproducible, precise, and economical approaches for the simultaneous estimation of dapagliflozin and linagliptin.

KEYWORDS: Dapagliflozin, Linagliptin, Simultaneous estimation, UV-Spectrophotometry, RP-HPLC

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INTRODUCTION [1-4,13]:

Diabetes mellitus is a chronic metabolic disease characterized by high blood glucose levels, caused by a deficiency in either insulin production or action, or both. These diseases are a global health problem, and combination therapy is often required to achieve optimal glycaemic control.

Dapagliflozin & **Linagliptin,** both are powerful drugs widely used in management of Type 2 diabetes mellitus. These drugs have distinct yet complimentary mechanism of action. The fixed dose combination of these two drugs was approved by **CDSCO** on **2nd of August 2023** for **Alkem Laboratories Ltd.**

Dapagliflozin: It is a highly selective sodium-glucose co-transporter-2 (SGLT-2) inhibitor. It works primarily in the proximal tubules of the kidneys, where it blocks the reabsorption of glucose back into the bloodstream. As a result, excess glucose is excreted through urine (a process known as glucosuria), which ultimately helps in lowering bloodglucose levels. In addition to improving glycemic control, dapagliflozin has been shown toprovide additional benefits such as modest weightloss and a reduction in blood

pressure, making it an important therapeutic option for patients with type 2 diabetes mellitus.

Linagliptin: It is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor. Its mechanism of action involves preventing the rapid breakdown of incretin hormones, including GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). These in cretin hormones play a key role in glucose homeostasis by stimulating insulin secretion and suppressing glucagon release from the pancreas, but only when blood glucose levels are elevated. By prolonging the activity of these hormones, linagliptin helps achieve better glycemic control without causing significant risk of hypoglycemia. Additionally, linagliptin is unique among DPP-4 inhibitors because it is largely excreted via the bile, making it suitable for patients with renal impairment. The combination of these drugs is beneficial because their complementary actions lead to better patient outcomes. This review article focuses on the analytical techniques, such as UV-Spectrophotometry and High- Performance Liquid Chromatography (HPLC) that have been developed and validated for the simultaneous estimation of these drugs in single formulations.

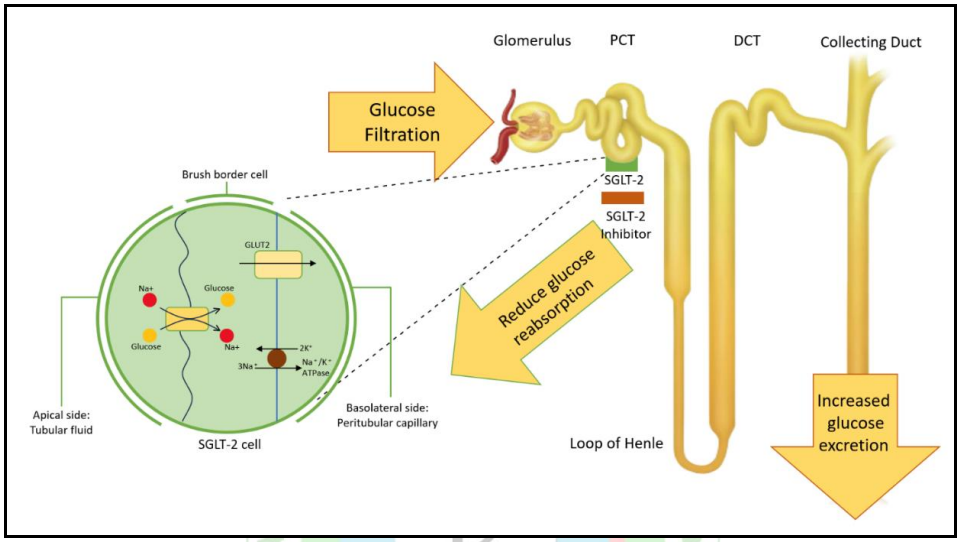


Figure 1: MOA of Dapagliflozin

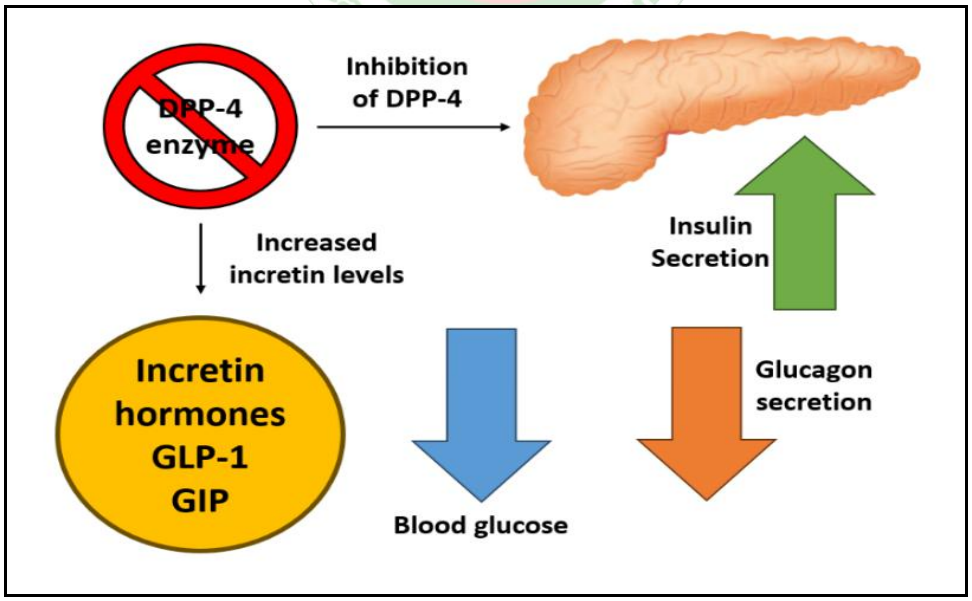
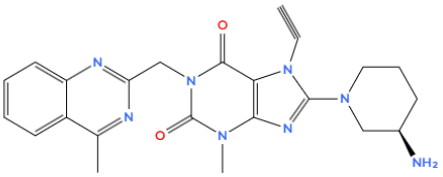
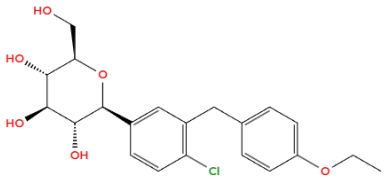


Figure 2: MOA of Linagliptin

DRUG PROFILE [5-13]:

Sr no.	Parameter	Linagliptin	Dapagliflozin
1	Structure		
2	IUPAC Name	8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione	(2S,3R,4R,5S,6R)-2-{4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl}-6-(hydroxymethyl) oxane-3,4,5-triol
3	Chemical formula	$C_{25}H_{28}N_8O_2$	$C_{21}H_{25}ClO_6$
4	Physical state	White or yellow solid	White to pale yellow solid
5	Molecular wt.	472.54 g/mol	408.88 g/mol
6	Class of drug	Type 2 diabetes mellitus	Type 2 diabetes, Heart failure
7	Mechanism of action (MOA)	DPP-4 inhibition → increase GLP-1 & GIP → increase insulin (glucose-dependent), decrease glucagon	SGLT2 inhibition → decrease glucose reabsorption in kidney → increase urinary glucose excretion → decrease plasma glucose
8	Half life	~12 hours	~12-13 hours
9	SolubilityProfile	Slightly soluble in water	Low aqueous solubility; soluble in organic solvents
10	Bioavailability	~30%	~78%
11	Melting Point	202-209 °C	55-58 °C
12	pKa Value	8.6 (basic),1.9	~13.2 (phenolic OH, Predicted)
13	Log P Value	1.7-2.8	2.9
14	CAS Number	668270-12-0	461432-26-8
15	Protein binding	~75-99%	~91%
16	Adverse effects	Cough,Headache, Hypoglycemia risk, Nasopharyngitis.	Dehydration, UTI, Lowering Genital-mycotic infection,
17	Brand name	Tradjenta®	Forxiga®, Farxiga®
18	Approval year	FDA 2011	EMA 2012; FDA 2014
19	CDSCO Approval year	2017	2015

REPORTED ANALYTICAL METHODS

HPLC: High performance liquid chromatography (HPLC) is a widely used analytical technique for separating, identifying and quantifying components in complex mixtures. It works by passing a liquid sample through a column packed with **stationary phase material**, where different compounds move at different speeds. Due to its high accuracy, sensitivity and reproductivity HPLC has become an essential tool in pharmaceutical, biomedical, food and environmental analysis.

UV- Visible spectroscopy: It is a simple and widely used analytical technique based on the **absorption** of Ultraviolet or visible light by molecules. The amount of light absorbed at specific wavelengths provides information about the concentration and structure of compounds. Due to its accuracy, rapid results and non-destructive nature UV-vis spectroscopy is extensively applied in pharmaceutical, biochemical and environmental studies.

HPTLC: High- Performance liquid Thin Layer Chromatography is an advanced from of Thin Layer Chromatography that allows precise, efficient, and reproducible separation of compounds. It uses a stationary phase coated on plates and enables simultaneous analysis of multiple samples with high sensitivity. HPTLC is widely used in pharmaceuticals, herbal drug standardization, food quality control and environmental studies.

Individual Estimation of Dapagliflozin

Sr. No.	Topic	Method	Description	Ref. No.
1	Dapagliflozin in Tablet Formulation	UV	**Solvent:** Methanol: Water. **Linearity:** 5-40 µg/mL. **λ:** 224 nm.	**14**
2	Dapagliflozin in Bulk and Tablet	UV	**Solvent:** Ethanol: Phosphate buffer (pH 7:2) (1:1 % v/v). **Linearity:** 10-35 µg/mL. **λ:** 233nm.	**15**
3	RP-HPLC Method for Tablet	RP-HPLC	**Stationary Phase:** Princeton C_{18} column. **Mobile Phase:** Acetonitrile: 0.1% Triethylamine (pH 5) (50:50% v/v). **Flow Rate:** 1 mL/min. **λ:** 224 nm.	**16**
4	Stability-Indicating RP-HPLC	RP-HPLC	**Stationary Phase:** Hypersil BDS C_{18} column (250mm×4.6mm, 5µm). **Mobile Phase:** Mobile phase-A (Buffer pH6.5), &Mobile phase-B (Acetonitrile: Water 90:10% v/v) **Flow Rate:** 1 mL/min. **λ:** 245 nm.	**17**
5	HPLC for API	HPLC	**Stationary Phase:** Agilent C_{18} column (4.6mm×150, 5µm). **Mobile Phase:** Acetonitrile: Dipotassium hydrogen phosphate (pH 6.5) (40:60% v/v). **Flow Rate:** 1 mL/min.	**18**
6	Stability-indicating RP-HPLC	RP-HPLC	**Stationary Phase:** BDS C_{18} column **Mobile Phase:** Acetonitrile: Orthophosphoric acid. **Flow Rate:** 1ml/min. **λ:**245 nm.	**19**
7	Dapagliflozin in its API & its tablet formulation	UV	**Solvent:** Methanol **Linearity:**0.5 - 2.5µg/mL. **λ:**226 nm.	**20**
8	RP-HPLC method & its degradation studies	RP-HPLC	**Stationary Phase:** Hypersil BDS C_{18} column (250mm×4.6mm, 5µm). **Mobile Phase:**Buffer: Acetonitrile(40:60% v/v). **Flow Rate:** 1ml/min. **λ:**245 nm.	**21**
9	HPTLC method for Bulk & tablet dosage form	HPTLC	**Stationary Phase:**Merck TLC Plates silica gel alumina plate (10×10cm) **Mobile Phase:** Chloroform: Mathanol (9:1%v/v) **Rf value:** 0.21±0.004 **λ:**223 nm.	**22**

Individual Estimation of Linagliptin

Sr. No.	Topic	Method	Description	Ref. no.
1	Linagliptin in Bulk Drug	UV	**Solvent:** Distilled water. **Linearity Rate:**1-10µg/ml. **λ:**295 nm.	**23**
2	Stability Indicating HPLC-DAD	HPLC	**Stationary Phase:** Zorbax eclipse XDB- C_{18} (4.6×150mm, 5µm) column. **Mobile Phase:** Methanol: Water (40:60% v/v). **Flow Rate:** 1 ml/min. **λ:** 225 nm.	**24**
3	Linagliptin in Bulk Drug	RP-HPLC	**Stationary Phase:** Phenomenex C_{18} Column **Mobile Phase:** Phosphate buffer: Methanol (50:50%) **Flow Rate:** 0.8mL/min. **λ:** 238 nm.	**25**
4	Linagliptin	UV	**Solvent:** Methanol **Linearity Rate:**5-30µg/ml. **λ:**294 nm.	**26**
5	Linagliptin	UV	**Solvent:** Methanol: water (15:85 v/v) **Linearity Rate:** 6-16µg/ml. **λ:**240 nm.	**27**
6	Linagliptin	UV	**Solvent:** Distilled water. **Linearity Rate:** 1-10µg/ml. **λ:**295 nm	**28**

Simultaneous Estimation Dapagliflozin and Linagliptin

Sr.No	Topic	Method	Properties	Ref. No.
1	RP-HPLC Method with PDA	RP-HPLC	**Stationary Phase:** Hypersil C_{18} column (250×4.6 mm, 5 µm). **Mobile Phase:** Acetonitrile: Water (90:10% v/v) (pH 3 adjusted with Ammonium Acetate) **Flow Rate:** 1 mL/min. **λ:** 244nm.	**29**
2	RP-HPLC Method Development	RP-HPLC	**Stationary Phase:** Qualisil 5 BDS C18 column (250×4.6mm,5µm). **Mobile Phase:** Acetonitrile: 0.1% O-Phosphoric acid (45:55% v/v) (pH 4 with adjusted TEA) **Flow Rate:** 1.0ml/min. **λ:** 239nm.	**30**
3	UV Spectrophotometry & HPLC	UV and HPLC	**UV Method:** At 295 nm (Dapagliflozin) and 225 nm (Linagliptin). **Solvent:** Water. **HPLC Method: Stationary Phase:** Thermo- Scientific Syncronis C8 column (250×4.6 mm, 5µm). **Mobile Phase:** 40:60 v/v of phosphate buffer and acetonitrile. **λ:** 235 nm.	**31**
4	RP-HPLC Method	RP-HPLC	**Stationary Phase:** Shim pack C_{18} (250mm×4.6 mm, 5µm). **Mobile Phase:** Phosphate buffer: Methanol sodium: ACN (40:30:30% v/v/v). **Flow Rate:** 1 mL/min. **λ:** 223 nm.	**32**
5	HPTLC method	HPTLC	**Stationary Phase:** Silica gel alumina plate 60 F254 (10×10cm) **Mobile Phase:** Chloroform: Methanol: ethyl acetate: 1% formic acid (3:4:3:0.5% v/v) **Rf value:** DAPA 0.66 & LINA 0.22 **λ:**224 nm.	**33**

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