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A Reviw Article on UV and HPLC Method for Dapagliflozin and Linagliptin in Synthetic Mixture.

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ABSTRACT
The type 2 Diabetes mellitus affects 90% of people with diabetes and causes high blood sugar level and other medical condition that are associated with it, including an increase risk of cardio vascular diseases, neurological and nephrological disease problem. The analytical method have been show in the literature, including UV spectroscopy, High performance liquid chromatography(HPLC). The combined use of dapagliflozin and linagliptin for managing T2DM is reasonable and attractive because of their different but complementary mechanism of action and separate path of degradation. The combination use of SGLT-2 inhibitor and DPP-4 inhibitor is significantly associated with a decrease in glycemic control, body weight and systolic blood pressure.
Keywords: Dapagliflozin, Linagliptin, HPLC, UV.

I. INTRODUCTION OF DISEASE.[1-4]

- Insulin is a hormone produced by the pancreas that regulates the amount of glucose in the blood. In diabetes mellitus, either the pancreas does not produce enough insulin or the body cannot effectively use the insulin that is produced.
- Type 1 diabetes is an autoimmune condition in which the immune system attacks and destroys the cells in the pancreas that produce insulin. Type 2 diabetes is a metabolic disorder that occurs when the body becomes resistant to insulin or when the pancreas cannot produce enough insulin to meet the body's needs.
- In people with type 2 diabetes, medications such as metformin, sulfonylureas, DPP-4 inhibitors, GLP-I receptor agonists, and SGLT2 inhibitors may be used to lower blood sugar levels.
- Regular monitoring of blood sugar levels is important for people with diabetes mellitus. In addition to HbA1c, other tests such as fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) may be used to diagnose diabetes or to monitor blood sugar control.

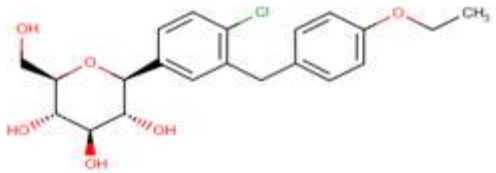

Fig:1 Chemical structure of Dapagliflozin

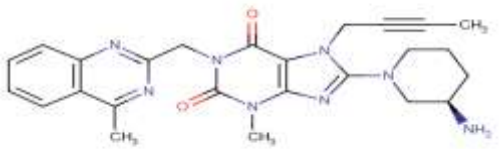

Fig: Chemical structure of Linagliptin.

Introduction of dapagliflozin.[5,6]

- On January 8, 2014 USFDA approved dapagliflozin to treat type 2 diabetes which was followed by approval to reduce the risk of hospitalization for HF in adult patients with type 2 diabetes and established CV disease or multiple CV risk factors in October 2019.
- Dapagliflozin (Forxiga) is one such SGLT2 inhibitor that is approved for the treatment of T2D in various countries worldwide, including the EU and USA.

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Mechanism of action of Dapagliflozin.[8]

- Dapagliflozin inhibits the sodium-glucose contransporter 2(SGLT2) which is primarily located in the proximal tubule of the nephron. SGLT2 facilitates 90% of glucose resorption in the kidneys and so its inhibition allows for glucose to be excreted in the urine. This excretion allows for better glycemic control and potentially weight loss in patients with type 2 diabetes mellitus.

Introduction of Linagliptin.[7]

- Linagliptin is an oral antihyperglycemic agent that selectively inhibits the enzyme dipeptidyl peptidase-4 (DPP-4).
- May 2,2011 USFDA approved Linagliptin for improving blood glucose control in adult with type 2 Diabetes.
- Linagliptin is a xanthine-based orally administered, potent, and long-acting non-peptidomimetic DPP-4 inhibitor that has been developed for treating T2DM.

Mechanism of action of Linagliptin.[9]

- Linagliptin is a competitive, reversible DPP-4 inhibitor. Inhibition of this enzyme slows the breakdown of GLP-1 and glucose-dependant insulinotropic polypeptide (GIP). GLP-1 and GIP stimulate the release of insulin from beta cells in the pancreas while inhibiting release of glucagon from pancreatic beta cells. These effects together reduce the breakdown of glycogen in the liver and increase insulin release in response to glucose.

Table:1Method for Determination of Dapagliflozin and Linagliptin single and combination with other drugs by UV Spectroscopy, chromatography and other

Sr.no.	Method	Description	Ref no.
1	Estimation of Dapagliflozin from its Tablet Formulation by UV-Spectrophotometry.	**Solvent:** Methanol: Water. **Linearity**: 5-40µg/ml. **METHOD-1** **wavelength:**224nm. **METHOD-2** **wavelength:**218-230nm. **METHOD-3** **wavelength:**220nm. **METHOD-4** **Detection wavelength:**224nm,235.5nm.	10
2	Unique UV Spectrophotometric method for Reckoning of Dapagliflozin in Bulk and Pharmaceutical Dosage form.	**Solvent:** Ethanol: Phosphate Buffer (ph-7.2) (1:1%v/v). **Linearity:**10-35 µg/ml **Detection wavelength:**233.65nm.	11
3	Development and validation of UV Spectroscopic method for Dapagliflozin in its API and its Tablet Formulation.	**Solvent:** Methanol **Linearity:**0.5-2.5µg/ml **Detection wavelength:**226nm	12
4	Development and Validation of UV Spectroscopic First Derivative method for simultaneous estimation of Dapagliflozin and Metformin Hydrochloride in Synthetic Mixture.	**Solvent:** Methanol **Linearity** **Dapagliflozin**: 0.5-2.5 µg/ml **Metformin hydrochloride :**25-125 µg/ml **Detection wavelength:** **Dapagliflozin:**235nm. **Metformin hydrochloride:**272nm	13

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5	Development and Validation of UV Spectroscopic Method for Simultaneous Estimation of Dapagliflozin and Metformin Hydrochloride in Synthetic Mixture.	**Solvent:** Methanol **Linearity:** **Dapagliflozin:**0.5-2.5 µg/ml **Metformin Hcl:**25-125 µg/ml **Detection wavelength:** **Dapagliflozin:** 225nm **Metformin Hcl:** 237nm	14
6	Development and Validation of UV Spectroscopic Method for Simultaneous Estimation of Dapagliflozin and Saxagliptin in Marketed Formulation.	**Solvent:**pH6.8 ofPhosphate Buffer **Linearity:** **Dapagliflozin:**5-25 µg/ml **Saxa:** 5-25 µg/ml **Detection wavelength:** **Dapagliflozin:**276nm **Saxa:**222nm	15
7	A Novel Method Development and Validation of Dapagliflozin and Metformin Hydrochloride 222 nm using Simultaneous Equation Method by UV– Visible Spectroscopy in Bulk and Combined Pharmaceutical Formulation including Forced Degradation Studies.	**Solvent- Water** **Detection Wavelength:** **Dapagliflozin:** 222 nm **Metformin:** 232 nm **Linearity-** **Dapagliflozin:** 2 - 32 µg/ml **Metformin:** 1 - 20µg/ml	16
8	RP-HPLC Method for Estimation of Dapagliflozin form its Tablet.	**Stationary phase:** Princeton C18 column. **Mobile phase**: Acetonitrile:0.1%Triethylamine (pH-5.0) (50:50%v/v). **Flow rate**:1ml/min. **Injected vol**: 20µl. **Detection wavelength**: 224nm	17
9	Development and validation of High-Performanceliquid Chromatographic Method for Determination of Dapagliflozin and its Impurities in Tablet Dosage Form.	**Stationary phase:** Hypersil BDS C18 column (250mm×4.6mm,5µm). **Mobile phase:** Mobile phase-A (Buffer pH-6.5) and Mobile phase-B (Acetonitrile: Water 90:10%v/v). **Flow rate:**1 ml/min. **Detection wavelength:**245nm.	18
10	Development and validation of stability-indicating RP-HPLC method for Determination of Dapagliflozin.	**Stationary phase:** BDSC18 column. **Mobile phase:** Acetonitrile: Orthophosphoric acid. **Flow rate:**1ml/min. **Injection vol**:10 µl **Detection wavelength:** 245nm.	19
11	Development and stability indicating HPLC for Dapagliflozin in API and Pharmaceutical Dosage Form.	**Stationary phase:** Agilent C18 column (4.6mm*150,5µm). **Mobile phase:**Acetonitrile: Dipotassium hydrogen phosphate (pH6.5with adjust OPA) (40:60%v/v). **Flow rate:**1ml/min.	20

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		Injection vol:10 µl **Detection wavelength:**222nm.	
12	Stability Indicating HPLC Method for the Simultaneous Determination of Dapagliflozin and Saxagliptin in Bulk and Tablet Dosage Form.	**Stationary phase**: Xterra C18 Column. (4.6*150mm,5µm) **Mobile phase**: Acetonitrile: Water (60:40 %v/v). **Flow rate**:1ml/min. **Injected vol**.: 20µl.	21
13	Development and Validation of RP-HPLC Method for Simultaneous Estimation of Dapagliflozin and Metformin in Bulk and in Synthetic Mixture.	**Stationary phase:**PhenomenexlunaC18 Column(4.6mm×250mm**,**5µm). **Mobile phase:** Acetonitrile: Water(75:25%v/v). **Flow rate**: 1ml/min. **Injected vol**:10 µl **Detection wavelength:**285nm.	22
14	A highly validated RP-HPLC method for the Simultaneous Estimation of Dapagliflozin and Saxagliptin in Tablet Dosage Form.	**Stationary phase:**BDS C8 Column (50*4.6mm,5µm). **Mobile phase**: KH_2PO_4: Acetonitrile (55:45%v/v). **Flow rate**:1ml/min. **Injection vol**:10µl **Detection wavelength**:210nm.	23
15	Development and validated stability indicating assay method for simultaneous estimation of Metformin and Dapagliflozin by RP-HPLC.	**Stationary phase:**C18 column (4.6×150mm,5µm). **Mobile phase:** Acetonitrile:0.1M Orthophosphoric acid. (70:30%v/v). **Flow rate**:1.0ml/min. **Detection wavelength**:260nm	24
16	Stability indicating HPLC Method for the Simultaneous Determination of Dapagliflozin and Sexagliptin in Bulk and Tablet Dosage Form.	**Stationary phase:** Xterra C18 column (4.6×150mm,5 µm). **Mobile phase:** Acetonitrile: Water (60:40%v/v). **Flow rate**:1ml/min. **Injection vol:** 20µl **Detection wavelength**:248nm.	25
17	A New High-Performance Thin Layer chromatographic method Development and Validation of Dapagliflozin in Bulk and tablet dosage form.	**HPTLC:** **Stationary phase:** Merck TLC plates silica gel aluminum plate (10×10CM). **Mobile phase:** Chloroform: Methanol(9:1%v/v). **R_F VALUE**: 0.21±0.004 **Detection wavelength**:223nm.	26
18	A Stability Indicating RP-HPLC Method Validation for Simultaneous Estimation of Metformin HCl, Dapagliflozin and Saxagliptin in Pharmaceutical Dosage Form.	**Mobile Phase:**Phosphate Buffer pH 3.5 and Acetonitrile (80:20 v/v%) + 1 ml Triethylamine per 100 ml Mobile phase **Stationary phase:**C18 column (250mm×4.6 mm), 5mm particle size **Detection Wavelength:** 265 nm **Flow Rate:** 1.0 ml/min	27
19	Analytical Method Development and Validation for Determination of Linagliptin in Bulk and Dosage Form by UV Spectroscopy.	**Solvent**: Distilled Water. **Linearity:** 1-10µg/ml. **Detection wavelength:**295nm.	28

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20	Development and Validation of UV spectrophotometric method for Simultaneous Estimation of Empagliflozin and Linagliptin in bulk drugs and pharmaceutical dosage form.	**Solvent:** Methanol **Linearity:** 5-80µg/ml. **Detection wavelength:** Empagliflozin:276nm, Linagliptin: 293nm.	29
21	RP-HPLC Method Development and Validation of Linagliptin in Bulk Drug and Pharmaceutical Dosage Form.	**Stationary phase:** Phenomenex C18column (4.6×100mm,5 µm). **Mobile phase**: Phosphate buffer: Methanol (50:50%v/v). **Flow rate:**0.8ml/min. **Injection vol:**20µl **Detection wavelength:**238nm.	30
22	Stability Indicating HPLC-DAD Method for the Determination of Linagliptin in Tablet Dosage Form: Application to Degradation kinetics.	**Stationary phase**: Zorbax eclipse XDB-C18(4.6×150MM,5µm) column. **Mobile phase**: Methanol: Water (40:60%v/v). **Flow rate**:1ml/min. **Detection wavelength**: 225nm.	31
23	Development and Validation of RP-HPLC Method for Simultaneous Estimation of Metformin and Linagliptin in Combined Pharmaceutical Dosage Form.	**Stationary phase**: hypersil-BDS C18 column (250mm×4.6mm),5µm. **Mobile phase**:KH_2PO_4 and Acetonitrile (40:60%v/v). **Flow rate**:1.0ml/min. **Detection wavelength:** 250nm	32
24	Analytical method Development and validation of Antidiabetic drug (Metformin and Linagliptin) in tablet dosage form by using RP-HPLC method.	**Stationary phase:** THERMO C18,250cm×4.6mm,5µm column. **Mobile phase**: KH_2PO_4 and Methanol (65:35%v/v). **Flow rate:**1.0ml/min. **Detection wavelength:** 226nm**.**	33
25	Development and Validation of a Stability-Indicating HPLC Method for Empagliflozin and Linagliptin in Tablet Dosage Form.	**Stationary phase:**C18 column (BDS 250mm×4.6mm,5 µm). **Mobile phase:**0.1% Orthophosphoric acid and Acetonitrile(60:40%v/v). **Flow rate**: 1ml/min. **Detection wavelength**:230nm	34
26	Development and Validation of RP-HPLC Method for the Simultaneous Estimation of Empagliflozin and Linagliptin in Solid Dosage Form.	**Stationary phase:** Thermo C18 column (250mm×4.6,5 µm). **Mobile phase**: Acetonitrile: Methanol (50:50%v/v). **Flow rate**:1ml/min. **Detection wavelength**: 280nm.	35
27	RP-HPLC Method for Simultaneous Estimation of Metformin and Linagliptin in Tablet Dosage Form.	**Stationary phase:** X-bridge C18 column (150×4.6mm,5 µm). **Mobile phase**: Acetonitrile: 0.02M Phosphate Buffer (ph 5.0) (35:65%v/v). **Flow rate:**1.0ml/min. **Injection vol:** 10 µl **Detection wavelength:**225 nm.	36
28	Simultaneous quantification of Empagliflozin, Linagliptin and Metformin Hydrochloride in Bulk	**Stationary Phase:** Phenomenex C18 Column (250mm×4.6mm,5 µm). **Mobile Phase:** Acetonitrile: Methanol:	37

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	and Synthetic Mixture by RP-HPLC Method.	Water (27:20:53%v/v/v) pH 4 adj. with 1%OPA. **Flow rate:** 1ml/min. **Injection vol:** 20µl **Detection wavelength:** 223nm	
29	New Validated Stability Indicating RP-HPLC Method for The Simultaneous Determination of Metformin Hydrochloride, Linagliptin and Empagliflozin in Bulk and Pharmaceutical Dosage Form.	**Stationary Phase:** Agilent Eclipse XDB-C18(250mm× 4.6mm, 5 µm). **Mobile Phase:** 0.1% Triethylamine(pH-3) Buffer: Acetonitrile (40:60%v/v) **Flow rate:** 1 ml/min **Injection vol:** 10 µl **Detection wavelength:** 240nm	38

Table: 2 Formulation of synthetic Mixture.

Sr.no	Ingredient	Quantity (mg)	Role
1	Linagliptin	5	API
2	Dapagliflozin	10	API
3	Microcrystalline cellulose	20	Disintegrate
4	Hydroxypropylmethylcellulose	15	Binder
5	Lactose monohydrate	20	Diluent
6	Magnesium stearate	10	Lubricant
7	Talc	20	Glidant
8	Total amount	100	-

II. CONCLUSION

- This review describes the reported Spectroscopic and Chromatographic methods developed Dapagliflozin and Linagliptin. As per this review, it was concluded that for Dapagliflozin and Linagliptin, different Spectroscopic and chromatographic methods are available for single-single drugs. It was observed that still, any combination method of Dapagliflozin and Linagliptin is not available.Thus, all methods were simple, accurate, economical, precise, and reproducible. Nearly all Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time, and sensitivity.

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