https://doi.org/10.46344/JBINO.2023.v12i03.11

A REVIEW ON ANALYTICAL METHODS FOR ESTIMATION OF DAPAGLIFLOZIN AND VILDAGLIPTIN IN BULK AND IN PHARMACEUTICAL COMBINED DOSAGE FORMS

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ABSTRACT

Dapagliflozin and Vildagliptin both are anti-diabetic medications used to treat people with type-2 diabetes mellitus. Dapagliflozin lowers blood glucose levels and enhances urine glucose excretion. Vildagliptin causes extended enzyme inhibition by forming a covalent bond with the DPP-4 catalytic site. When a single medication is ineffective for treating high blood sugar, Vildagliptin and Dapagliflozin are both administered in combination. Numerous analytical techniques, including UV, HPLC, LC-MS, and HPTLC approaches, have been developed for the determination of Dapagliflozin and Vildagliptin in pharmaceutical dosage form and bulk form. The study that follows shows a review of analytical techniques that covers estimating type-2 diabetic medication.

Keywords: Dapagliflozin, Vildagliptin, UV-spectroscopy, RP-HPLC.

INTRODUCTION:

IUPAC name for Dapagliflozin (2s, 3R, 4R, 5R, 6R)2 [4-Chloro-3 [4-ethoxybenzyl] phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.Dimethyl formamide, DMSO, and ethanol all make it soluble. It is only weakly soluble in aqueous buffer and water. The major purpose of it is to cure type-2 diabetes. Heart failure can also be treated with it. Positive side effects of Dapagliflozin include a decrease in body weight, a decrease in blood pressure, an increase in hemoglobin [1], and a decrease in high-sensitivity cardiac troponin. The European Medicines Agency's (EMA) Biologics Classification System (BCS) classifies Dapagliflozin as a Category III diabetes medication. These inhibitors constitute a new class of almost impermeable, more soluble anti-diabetic medications termed flozins [2]. Recent research has demonstrated that Dapagliflozin has a rapid onset of effect and lowers fasting plasma glucose levels within one week of treatment[3]. Dapagliflozin inhibits the Sodium Glucose Co Transporter 2 (SGLT 2) with high specificity.

It works by preventing the kidneys from reabsorbing glucose, which causes the excess to be excreted in the urine and improves glycemic control in people with type 2 diabetes[4].The chemical name for Vildagliptin is (S)-1-[(3-hydroxyadamantan-1-yl) amino] acetyl pyrrolidine-2-carbonitrile. In water, methanol, ethanol, DMSO, and dimethyl formamide, it is freely soluble. Vildagliptin is a type 2 diabetic mellitus (T2DM) drug that inhibits the dipeptidyl peptidase-4 (DPP-4) enzyme. The ability of DPP-4 inhibitors to raise the levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide [5] (GIP) in the systemic circulation determines how they inhibit DPP-4.

Vildagliptin thus reduces unneeded glucagon release in T2DM patients and enhances insulin secretion in them. In addition, it lowers HbA1c when used with one of the other regularly prescribed classes of oral hypoglycemic medications: thiazolidinedione, sulfonylurea, or insulin, without causing weight gain or severe hypoglycemia. [6] Vildagliptin is quickly absorbed when taken by mouth. Vildagliptin is metabolised via hydrolysis to an extent of around 70%, and renal excretion accounts for 85% of its excretion, with 23% of the oral dose ending up in the urine unmodified. Food consumption has no impact on the drug's pharmacokinetics [7]. The main P450 enzymes are neither inhibited nor induced by it.

Table 1: Methods for determination of Dapagliflozin single and combination with other drugs by UV Spectroscopy, Chromatography and other techniques

S.NO	DRUGS	METHOD	DESCRIPTION	REF .NO
1.	**Dapagliflozin in pharmaceutial dosage form**	**RP-HPLC**	**Detective wavelength**:235nm **Mobile Phase:** Methanol: water (80:20) **Linearity range:**50-90 µg/ml **Correlation coefficient** :0.9998 **LOD:**0.0817 µg/ml **LOQ**:0.247µg/ml	**8**
2.	**Dapagliflozin, Saxagliptin and Metformin**	**Stability indicating HPLC Method (Bulk and pharmaceutical dosage form)**	**Detective Wavelength :**230nm **Mobile Phase:** Phosphate buffer: Acetonitrile (60:40) **Linearity range:** Dapagliflozin 1.25-7.5µg/ml Saxagliptin- 0.623-3.75µg/ml Metformin 125-750µg/ml **Correlation coefficient:** Dapagliflozin -0.999 Saxagliptin -0.999 Metformin-0.999 **%Recovery:** Found in between-98.51-100.80	**9**
3.	**Dapagliflozin,**	**RP-HPLC**		**10**

	and Metformin	**METHOD (Bulk and combined formulation)**	**Detective Wavelength :**230nm **Mobile Phase:** water: methanol **(50:50)** **Linearity range:** Dapagliflozin 0.6-0.21µg/ml Metformin 0.002-0,007µg/ml **Correlation coefficient:** Dapagliflozin -0.999 Saxagliptin -0.999 **%Recovery** Dapagliflozin –99.73% Saxagliptin -99.85%	
4.	**Dapagliflozin and Saxagliptin**	**UV Spectrophotometric Method**	**Detective Wavelength :**274nmand 224nm **Mobile Phase:**Methanol:water **Linearity range:**2-10µg/ml **Correlation coefficient:** Dapagliflozin -0.998 Saxagliptin -0.997 **LOD**: Dapagliflozin -0.1230µg/ml Saxagliptin -0.040µg/ml **LOQ:** Dapagliflozin -0.5460µg/ml Saxagliptin -0.01230µg	11
5.	**Dapagliflozin and Saxagliptin**	**HPLC Method and UV method**	**Detective Wavelength :**254nm **Mobile Phase:**0.1 %phosphoric acid and acetonitrile (50:50) **Linearity range:**0.05-2µg/ml And 0.01-0.5µg/ml **Correlation coefficient:** Dapagliflozin -0.998 Saxagliptin -0.998 **%Recovery** Dapagliflozin –81.458% Saxagliptin -78.689%	**12**

6.	**Dapagliflozin and Saxagliptin**	**UV Spectrophotometric Method**	**Detective Wavelength :**222nm and 276nm **Mobile Phase:** Phosphate buffer **Linearity range:**5-25µg/ml **Correlation coefficient:** Dapagliflozin -0.999 Saxagliptin -0.999 **LOD**: Dapagliflozin -0.95µg/ml Saxagliptin -1.23µg/ml **LOQ:** Dapagliflozin -2.72µg/ml Saxagliptin -3.25µg/ml	**13**
7.	**Dapagliflozin and Saxagliptin**	**RP-HPLC Method (Tablet dosage form)**	**Detective Wavelength :**225nm **Mobile Phase:** Methanol: Phosphate buffer **Linearity range:** Dapagliflozin 4-24µg/ml Saxagliptin- 2-12µg/ml **Correlation coefficient:** Dapagliflozin -0.999 Saxagliptin -0.998	**14**
8.	**Dapagliflozin and Saxagliptin**	**Stability indicating HPLC Method**	**Detective Wavelength :**248nm **Mobile Phase:** Acetonitrile: Water (60:40) **Linearity range:** Dapagliflozin 100-500µg/ml Saxagliptin-50-250µg/ml **Correlation coefficient:** Dapagliflozin -0.9998 Saxagliptin -0.9998 **LOD**: Dapagliflozin -3.00µg/ml Saxagliptin -3.02µg/ml **LOQ:** Dapagliflozin -9.98µg/ml Saxagliptin -10.01µg/ml	**15**

9	**Dapagliflozin in Bulk and Tablet Formulation**	**RP-HPLC Method**	**Wavelength:**210nm **Mobile phase:** 0.1%Orthophosphoricacidbuffer :Acetonitrile(60:40%v/v) **Flow rate :**1 ml/min **Injection volume :** 10 µL **Runtime:** 5min **Retentiontime:**2.226min **Linearity range** :25–150µg/ml **%Recovery**: 98.95–101.72% **%RSDintradayprecision:**0.6% **%RSDinterdayprecision:**0.4%	**16**
10	**Saxagliptin and Dapagliflozin in bulk and dosage forms**	**Stability indicating RP-HPLC method**	**Wavelength:**225 nm **Mobile phase :** Phosphate Buffer **:**Acetonitrile (50:50 v/v) **Flow rate :**1.2 mL/ min **Linearity range :**Saxagliptin 20-60 µg/ml **Dapagliflozin:**40-120µg/ml **Retention time:** Saxagliptin 2.1 min Dapagliflozin 2.8 min **Accuracy range:** 99.99-100.50 % **Precision :** Saxagliptin 0.78 % Dapagliflozin 0.44% **LOD :** Saxagliptin 1.63 µg/ml Dapagliflozin 1.94 µg/ml **LOQ :** Saxagliptin 5.39 µg/ml Dapagliflozin6.50 µg/ml **% Assay:**100.24-100.43 **%**	**17**
11	**Saxagliptin Hydrochloride and Dapagliflozin in bulk and in tablet form**	**Stability indicating RP-HPLC method**	**Wavelength:220 nm Mobile phase :**Potassium dihydrogen phosphate Buffer (pH 6.0) : Acetonitrile (45:55 v/v) **Linearity range :** Saxagliptin HCl 56-84 µg/ml Dapagliflozin 112-168 µg/ml	**18**
	Dapagliflozin		**Wavelength:**230nm **Mobile phase:**	

12	**and Saxagliptin in fixed- dose combination.**	**RP-HPLC method**	odium dihydrogen phosphate: Acetonitrile (53:47 v/v) **Flow rate :** 1.2 mL / min **Linearityrange**:2–14µg/mL	**19**
13	**Metformin and Dapagliflozin in bulk and synthetic mixture**	**RP-HPLC method**	**Wavelength:**285nm **Mobile phase:** Acetonitrile: Water(75:25%v/v) **Flow rate :**1ml/min **Injection volume :**10µl **Retention time** Metformin-3.2 min Dapagliflozin-5.4 min **Linearity range :** Metformin-20-100µg/ml Dapagliflozin-10-50µg/ml **%Recovery**:99.3-99.6% **LOD:** Metformin-5.0µg/ml Dapagliflozin-3.7µg/ml **LOQ :** Metformin-15.2µg/ml Dapagliflozin-11.42µg/ml	**20**
14	**Dapagliflozin in API.**	**RP-HPLC and UV-Spectroscopy.**	**Wavelength:**203nm **Mobile phase:** Acetonitrile: Orthophosphoric acid (55:45%) **Linearity range:** InHPLC-25-150µg/ml In UV-1-5 µg/ml **Correlationco-efficient:**0.999 **LOD :**0.01µg/ml **LOQ**:0.05µg/ml	**21**
15	**Dapagliflozin in blet formulation**	**UV Spectrophotom etric Method**	**Detectionwavelength:**224 nm **Mobile phase** Methanol: Water **Linearityrange:**5-40µg/ml **Correlation coefficient:**<1	**22**
16	**Dapagliflozin and Metformin**	**UV Spectrophoto metric Method**	**Detective Wavelength :**225nm and 237nm **Mobile Phase:** Methanol: HCL **Linearity range:**0.5-2.5µg/ml **Correlation coefficient:** Dapagliflozin -0.983 Metformin-0.985	**23**

17	**Dapagliflozin In bulk and pharmaceutical dosage forms**	**UV Spectrophotometric Method**	**Detectionwavelength:**233.65nm **Mobile Phase:** Ethanol: Phosphate buffer (1:1) **Linearity range:**10-35 µg/ml **Correlationcoefficient:**0.9998 **%Recovery:**99.7 **LOD:**1.24 µg/ml **LOQ:**3.62 µg/ml	**24**
18	**First derivative for simultaneous estimation of Dapagliflozin and Metformin HCL in synthetic mixture**	**UV Spectrophotometric Method**	**Wavelength:** Dapagliflozin-235 nm Metformin HCl-272 nm **Solvent :**Methanol **Linearity range :** Dapagliflozin-0.5-2.5µg/ml Metformin-25-125 µg/ml **Correlation co-efficient :** Dapagliflozin-0.980 Metformin HCl-0.982 **LOD:** Dapagliflozin-0.009µg/ml MetforminHCl-0.013µg/ml **LOQ :** Dapagliflozin-0.039µg/ml MetforminHCl-0.041µg/ml	**25**
19	**Dapagliflozin in bulk and tablet dosage form.**	**RP-HPLC method**	**Wavelength:**237nm **Mobile phase:** Phosphate buffer: acetonitrile (75:25% v/v) **Flow rate :**1.0 ml min-1 **Retention time** : 3.461min **Linearityrange**:10-60µg/ml **LOD** : 0.02 µg/ml **LOQ**: 0.06µg/ml	**26**
	Metformin		**Wavelength :**240nm **Mobile phase :**Phosphate Buffer(pH6.5): Methanol: Acetonitrile In the ratio of 50:30:20 v/v/v **Flow rate :**1 ml/min **RetentionTime :**MetforminHCL-2.475min Dapagliflozin-3.647 min **Linearity range :**	

20	**Hydrochloride and Dapagliflozin in tablet dosage form.**	**RP-HPLC method**	MetforminHCL85-510µg/ml Dapagliflozin 0.5–3µg/ml **LOD:** MetforminHCL-2.469ppm Dapagliflozin-3.650 ppm **LOQ :** MetforminHCl-2.468ppm Dapagliflozin-3.649 ppm **Correlation co-efficient:** MetforminHCl-0.997 Dapagliflozin-0.9973 **%Recovery:** MetforminHCl-100.67% Dapagliflozin-99.54%	**27**

Table 2: Methods for determination of Vildagliptin Single and combination with other drugs by UV Spectroscopy, Chromatography and other techniques

S.No	DRUGS	METHOD	DESCRIPTION	REF .NO
1.	**Remogliflozin Etabonate, Vildagliptin and Metformin Hydrochloride ombined dosage form**	**UV-Method and RP-HPLC Method**	**Wavelength:** Vildagliptin-202.75nm Metformin-226.76nm Remogliflozin-238.65nm **Mobile phase:** Acetonitrile: methanol :water (60:10:30) **Flow rate:** 1.0 mL/ min. **Linearity range :** Vildagliptin-1-5µg/ml Remogliflozin-2-10µg/ml Metformin-10-50µg/ml **LOD and LOQ** Vildagliptin-0.262-0.796 Remogliflozin-0.199-0.605 Metformin-0.0815-0.2471	**28**
2.	**Vildagliptin**	**HPLC-MS**	**Mobile Phase:** Water: Methanol(55:45) **Linearity range:** 0.05-2µg/ml and 0.01-0.5µg/ml **Correlation coefficient:** Vildagliptin-0.9990 **%Recovery** Vildagliptin-93.70-108.63%	**29**

3.	**Vildagliptin**	**UV-visible spectrophotometric (Gastric medium)**	**Wavelength:**210nm **Linearity range:** Vildagliptin - 5-60µg/ml **Correlation coefficient:** Vildagliptin-0.999 **%Recovery** Vildagliptin - 98-101% **LOD** Vildagliptin-0.951µg/ml **LOQ** Vildagliptin-2.513µg/ml	**30**
4.	**Vildagliptin**	**HPTLC Method(Bulk and Pharmaceutical dosage form)**	**Wavelength:**227nm **Linearity:**2000-20000ng/ml **Mobile phase:** Chloroform: n-Butanol: Methanol (5:2:3v/v/v) **%Recovery**:99.066 **LOD** Vildagliptin:357.31ng/ml **LOQ** Vildagliptin-1082.76ng/ml	**31**
5.	**Vildagliptin**	**Spectrophotometric method(Bulk and pharmaceutical dosage forms)**	**Wavelength:**202.5nm **Mobile phase:** 0.5 M HCL **Flow rate :**0.8 ml/min **Linearity range:** Vildagliptin-10-40µg/ml **Correlation coefficient:** Vildagliptin-0.999 **%Recovery** Vildagliptin- 100.17% **LOD** Vildagliptin-0.055µg/ml **LOQ** Vildagliptin-0.166µg/ml	**32**
6.	**`Vildagliptin and Metformin**	**RP-HPLC(Bulk and Pharmaceutical dosage forms)**	**Wavelength:**258nm **Mobile phase:** 0.1 M Potassium hydrogen phosphate: Methanol (60:40 %v/v) **Flow rate :**0.5 ml/min **Retention Time:**	**33**

			Metformin-1.43min Vildagliptin—5.32min **Linearity range:** Metformin-50-150 µg/ml Vildagliptin-50150µg/ml **%Recovery:** Metformin 100% Vildagliptin-100% **LOD** Metformin-0.005µg/ml Vildagliptin-0.0015µg/ml **LOQ** Metformin-0.014µg/ml Vildagliptin-0.0043µg/ml	
7.	**Vildagliptin and Metformin(Pharmaceutical dosage form)**	**RP-HPLC**	**Wavelength:**239nm **Mobile phase:** Acetonitrile: phosphate buffer: water (65:20:15 %v/v/v) **Flow rate :**1.0 ml/min **Linearity range :** Metformin-8-54 µg/ml Vildagliptin-4-34 µg/ml **%Recovery:** Metformin -99.9 % Vildagliptin-99.7% **LOD** Metformin-0.025µg/ml Vildagliptin-0.0040µg/ml	**34**
8.	**Vildagliptin And Application for study**	**UV-Spectroscopy and RP-HPLC** **(Second order Derivative)**	**Wavelength:**207nm **Mobile phase:** Potassium phosphate buffer:Acetonitrile (85:15% v/v) **Linearityrange:** Vildagliptin-25-125µg/ml	**35**

9.	**Vildagliptin**	**RP-HPLC (Bulk and Dosage form)**	**Wavelength:**207nm **Mobile phase:** Methanol:water (60:40v/v) **Flow rate :** 0.8 ml/min **Retentiontime:**3.58min **Linearity range :** Vildagliptin-10--60 µg/ml **%Recovery** Vildagliptin-99.56% **LOD** Vildagliptin-0.98µg/ml **LOQ** Vildagliptin-2.98µg/ml	**36**
10.	**Vildagliptin**	**HPLC method**	**Wavelength:**263nm **Retentiontime:**2.6min **Linearity:**50-175µg/ml **Mobile phase:** 0.OM Potassium dihydrogen: Phosphate buffer acetonitrile (80:20 v/v) **LOD** Vildagliptin-0.0182µg/ml **LOQ** Vildagliptin-0.0553µg/ml	**37**
11.	**Vildagliptin**	**UV-Spectrophotometer**	**Wavelength:**216nm **Linearity range :** Vildagliptin - 10-100µg/ml **Correlation coefficient:** Vildagliptin-0.997 **%Recovery** Vildagliptin– 99.83%	**38**

12.	**Vildagliptin**	**RP-HPLC Method(QBD approach and its application to forced degradation studies)**	**Wavelength:**210nm **Mobile phase:** Buffer:Acetonitrile: Methanol (70:10:20 v/v) **Flow rate :**1 ml/min **Linearity range :** Vildagliptin-5-15µg/ml **Correlation coefficient:** Vildagliptin-0.999 **%Recovery** Vildagliptin-99.56% **LOD** Vildagliptin-200ng/ml **LOQ** Vildagliptin-600ng/ml	**39**
13.	**Vildagliptin and Linagliptin**	**UV-Spectrophotometric method(Bulk and Pharmaceutical dosage forms)**	**Wavelength:** Vildagliptin-197nm Linagliptin-294nm **Linearity range :** Vildagliptin–8-32µg/ml Linagliptin-5-25µg/ml **Correlation coefficient:** Vildagliptin-0.999 **LOD** Vildagliptin-0.734µg/ml Linagliptin-0.247µg/ml **LOQ** Vildagliptin-2.224µg/ml Linagliptin-0.748µg/ml	**40**

CONCLUSION:

This review depicts the reported Spectroscopic and chromatographic methods developed and validated for estimation of Dapagliflozin and Vildagliptin. According to this review it was concluded that for Dapagliflozin and Vildagliptin different spectroscopic and chromatographic methods are available for single and combination also it was found that the mobile phase containing phosphate buffer, methanol, Acetonitrile, potassium dihydrogen were common for most of the chromatographic method to provide more resolution .It was observed that combination of Dapagliflozin and Vildagliptin were not found and most common combination of Dapagliflozin ,saxagliptin, vildagliptin and metformin .For chromatographic method flow rate is observed in the range 0.5 -1.2 ml/min to get good resolution time. For most of the spectroscopic methods common solvent is Methanol. Hence this all methods found to be simple, accurate, precise and

reproducible in nature. Most of the methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time and sensitivity.

ACKNOWLEDGEMENT:

We are thankful to Sarojini Naidu Vanita Pharmacy Maha Vidyalaya for supporting and encouraging us to carry out the review.

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