

ANALYTICAL METHODS AND VALIDATION OF MIGLITOL AND VOGLIBOSE: AN OVERVIEW

Abstract

Diabetes mellitus (DM) is a metabolic condition caused by problems with insulin secretion or activity that affects protein, lipid, and carbohydrate metabolism. As the disease progresses, severe diabetes side effects such as retinopathy, neuropathy, nephropathy, cardiovascular problems, and ulceration may emerge. Type 1 and Type 2 Diabetes mellitus, the two main kinds, have different pathogenic characteristics. T1DM is characterised by a failure to produce enough insulin because of the loss of pancreatic beta cells, which is frequently linked to autoimmune disease. T2DM increases the risk of microvascular and macrovascular problems due to insulin resistance and reduced insulin production. Various anti-diabetic drug classes, such as alpha-glucosidase inhibitors like miglitol and voglibose for the control of T2DM, are available as treatment alternatives. These drugs lower carbohydrate absorption, lowering postprandial blood glucose levels. The identification, classification, and determination of drug compounds and products are made possible by analytical method and validation, which are essential in the field of pharmaceutical research. The application of the analytical method is validated to confirm that it is suitable and secure for a certain purpose. Spectroscopic method such as UV-Visible spectroscopy, chromatographic method including HPLC, UPLC and hyphenated methods including LC-MS, LC-FD, LC-FD are employed as analytical method and validation techniques for drug miglitol and voglibose.

Keywords: Analytical method, Validation, Miglitol, Voglibose, Diabetes Mellitus

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I. INTRODUCTION

- 1. Diabetes Mellitus:** Diabetes mellitus (DM) is a metabolic disease caused by a problem with the release of insulin, its action, or both. Chronic hyperglycemia caused by insulin deficiency also creates issues with protein, lipid, and the breakdown of carbohydrates. Tissue or vascular damage develops when the illness increases, which can result in serious diabetic side effects such as retinopathy, neuropathy, kidney disease, cardiovascular issues, and ulcers [1]. Although the two main etiopathogenetic categories of type 1 diabetes and type 2 diabetes account for most diabetes cases [2].

Type 1 diabetes mellitus, also known as autoimmune diabetes, is a chronic illness that produces hyperglycemia due to an inability to produce adequate insulin due to the loss of pancreatic beta cells [3, 4].

Insulin resistance and reduced insulin secretion are the most common anomalies in T2DM. People with T2DM are at a high risk for both microvascular and macrovascular problems due to hyperglycemia and some aspects of the insulin resistance (metabolic) syndrome [5-7].

Anti-diabetic drugs are classified into several types, and the decision is influenced by the type of diabetes, the patient's age and circumstances, among other factors. Treatment possibilities include medicines that increase pancreatic insulin production, increase insulin sensitivity in target organs, and decrease glucose absorption from the gastrointestinal tract [8-10].

Oral hypoglycaemic agents include thiazolidinediones, biguanides, alpha glucosidase, DPP-IV inhibitors etc for a treatment of T2DM [11-16].

- 2. Alpha Glucosidase Inhibitor:** A type of anti-diabetic medicine known as alpha-glucosidase inhibitors (AGIs) is used to treat type 2 diabetes mellitus. They hinder the gut's ability to absorb carbohydrates, a complex form of sugar. AGIs are a distinct class of oral hypoglycaemic medications (OHAs) that have been authorised for the management and prevention of T2DM. Acarbose, miglitol, and voglibose are the three types of AGIs that are currently offered for the treatment of T2DM. All three AGIs work by vying with oligosaccharides in the brush border of the small intestine for the binding of the active centres of the α -glucosidase enzyme. By preventing postprandial glycemia peaks and delaying the rate of digestion of consumed carbohydrates, this decreases postprandial blood glucose and insulin levels [17-21].
 - **Miglitol:** An α -glucosidase inhibitor, miglitol reduces postprandial glucose concentrations, which are closely connected with the amount of carbohydrates in the diet. Miglitol works by delaying the absorption of complex carbohydrates in the small intestine. Miglitol side effects include gas, diarrhoea, and abdominal pain; they are minor and temporary [22].

Pharmacokinetics of miglitol: When used as monotherapy, miglitol is typically well tolerated and is not linked to body weight increase or hypoglycemia. The medication is quickly eliminated from the body via the kidneys without being metabolised in any

way. Although miglitol is not linked to hypoglycemia, concurrent usage with other oral antidiabetic medications could be reason for changing the dosage of those medications. In long-term investigations, miglitol demonstrated no appreciable effects on renal, respiratory, cardiovascular, or haematological indicators [23].

- **Voglibose:** Since 1994, it has been a commercially viable DM treatment in Japan. Voglibose's anti-hypoglycaemic effect is caused by a reversible suppression of the glycosidase hydrolyse enzymes in the brush border of the small intestine, which hydrolyse oligosaccharides and disaccharides to glucose and other monosaccharides. Voglibose inhibits the digestion and absorption of dietary polysaccharides by temporarily impeding the activity of enzymes that break down carbohydrates, such as maltase, sucrose, and zomaltase [24].

Pharmacokinetics of voglibose: After oral treatment, voglibose is slowly and ineffectively absorbed; at therapeutic dosages, plasma concentrations are typically undetectable. After intake, most of the active, unaltered medicine is still present in the lumen of the digestive tract, where intestinal enzymes and microbial flora break it down. To yet, no active metabolites have been found. Voglibose has a minimal renal excretion and is promptly eliminated in faeces [25].

3. Analytical Method Development and Validation

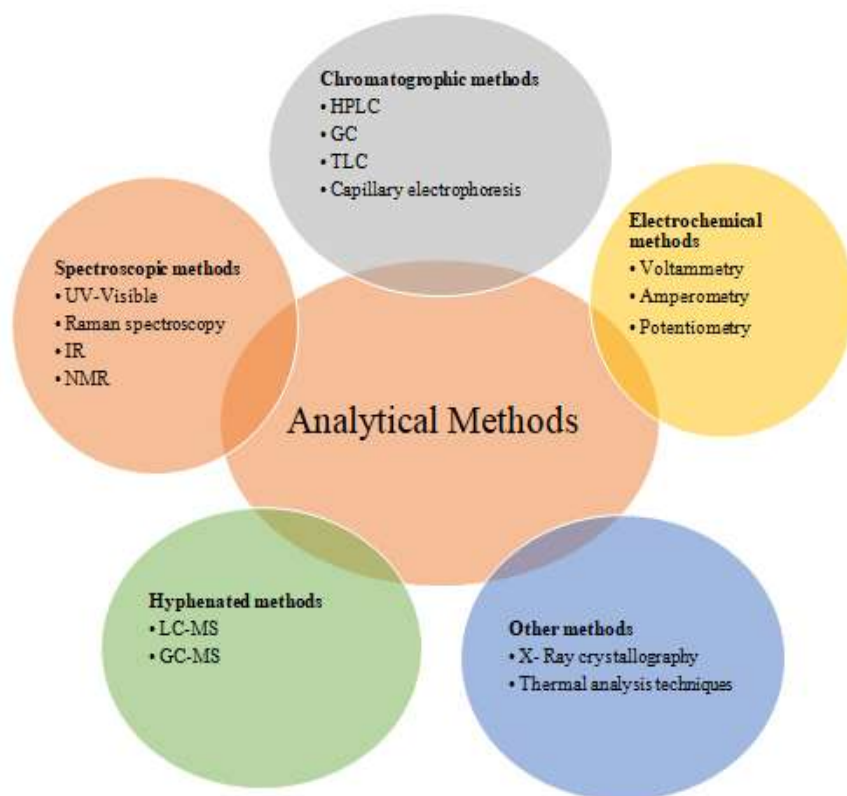


Figure 1: General analytical methods

- **Analytical Method Development:** The development and validation of analytical methods is critical to the discovery, development, and manufacture of pharmaceuticals[26]. An analytical technique is meant to compare a specific property of the drug substance or drug products to predetermined acceptance criteria for that characteristic[27]. Various analytical methods are shown in Figure 1. Development of analytical methods is the process of choosing an exact assay method to ascertain a formulation's composition [28].
- **Purpose of Analytical Method Development:** Drug analysis involves the identification, classification, and determination of pharmaceuticals in combinations such as dosage forms and biological fluids. The fundamental purpose of analytical methods employed in manufacturing and medication development is to offer information about potency, impurity, bioavailability, stability, and the effect of manufacturing parameters in order to ensure that the product is as safe as feasible[29]. Figure 2 consisting of steps of method development.

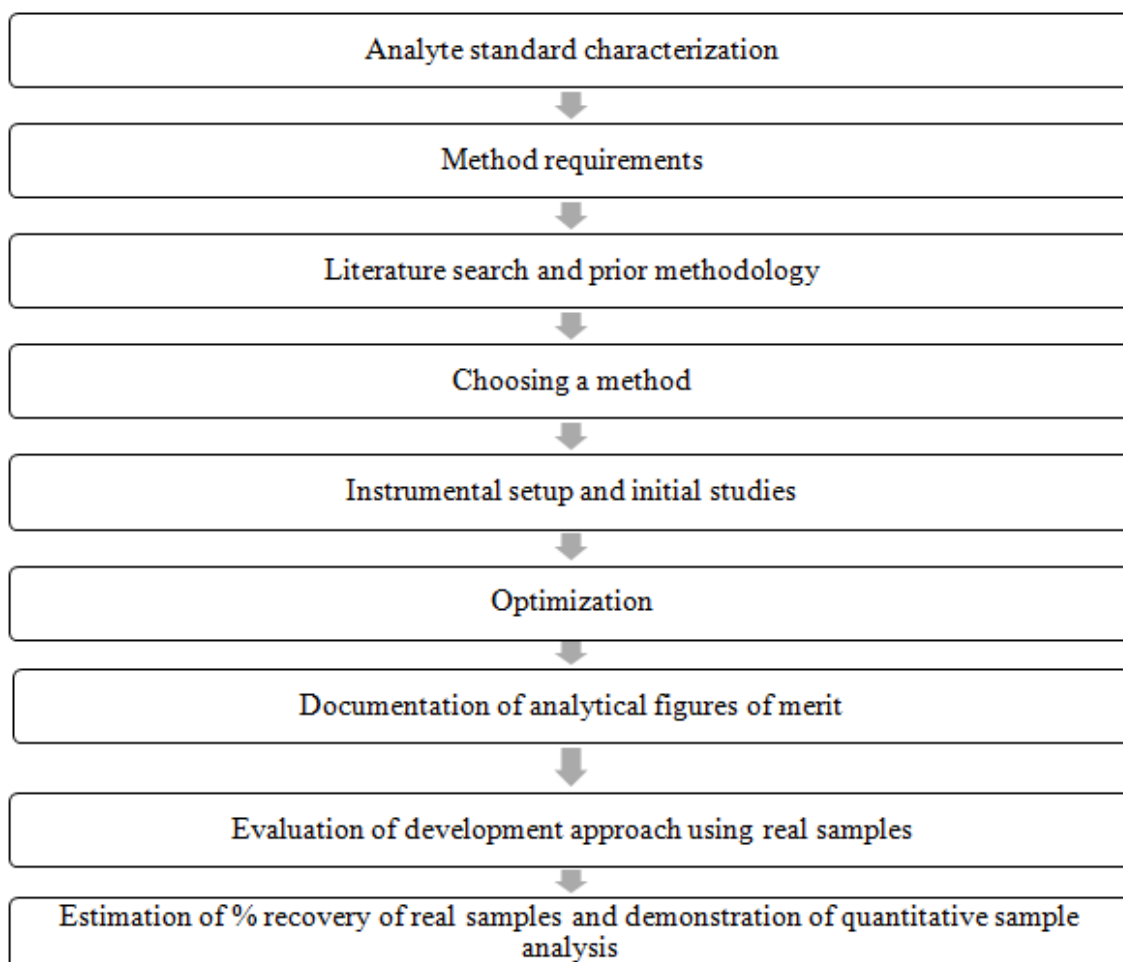


Figure 2: Steps of method development

Developed method must be validated. To do this, "Analytical Instrument Qualification" must first be carried out, which entails four primary phases: design

qualification, installation qualification, operational qualification, and performance qualification [30].

- **Validation:** The objective of validating an analytical method is to demonstrate that it is appropriate for the task at hand. Typical validation criteria recommended by the FDA, USP, and ICH are shown in Figure 3 [31].

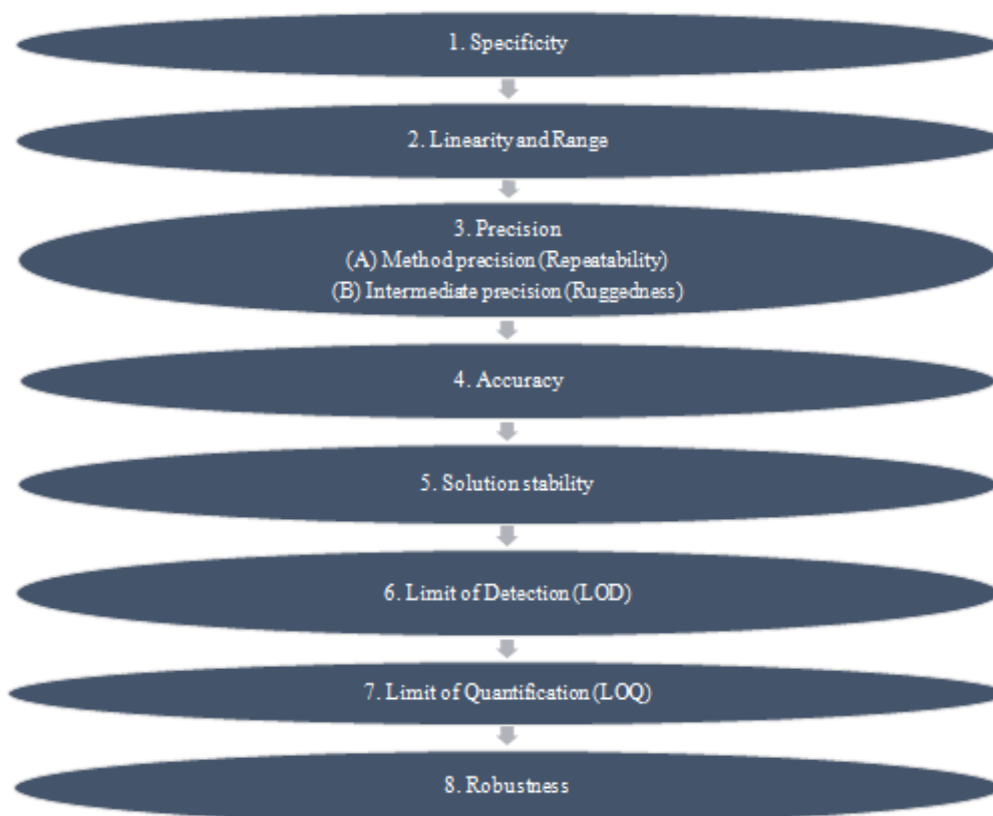


Figure 3: Validation parameters

4. Spectrophotometric Method

- **UV-Visible spectroscopy as analytical method for miglitol and voglibose [32-34]:** UV-VIS spectroscopy is a spectrophotometric technique that measures the intensity of light as a function of wavelength in the UV (100-400 nm) and VIS (400-800 nm) regions. It is regarded as the oldest analytical technique. After the analyte absorbs light of a specific wavelength of UV and VIS only, the amount of radiation absorbed by the analyte is measured. The interaction of UV-VIS EMR with the analyte produces the spectrum after UV-VIS light has been absorbed.
- **Principle:** UV-VIS spectroscopy, which is based on the phenomenon of light absorption, assesses the concentration of analytes in a sample solution by measuring the amount of absorbed light. Absorption increases as analyte concentration increases.

- **Electronic Transitions:** The absorption of electronic energy levels by an organic molecule is linked to the stimulation of valence electrons from the ground state to the excited state. After energy absorption, electronic transitions normally occur from the excited state, which possesses the highest molecular orbital. UV Visible spectroscopy of miglitol and voglibose are shown in Table No. 1

Figure 4: Components of UV-VIS Spectrophotometer

Table No. 1: UV Visible spectroscopy of miglitol and voglibose

Drugs	Solvent	λ_{max}	Linearity($\mu\text{g}/\text{ml}$)	LOD($\mu\text{g}/\text{ml}$)	LOQ($\mu\text{g}/\text{ml}$)	Ref
Voglibose	Methanol (taurine & sodium periodate)	282nm	10-80 $\mu\text{g}/\text{ml}$.	-	-	[35]
Miglitol + Acarbose	-	525nm and 610 nm	-	0.179 (Miglitol) 0.269 (Acarbose)	0.189 (Miglitol) 0.630 (Acarbose)	[36]
Miglitol + metformin	-	300nm, 270nm, 240nm and 210nm	0.2-1.2 (miglitol) 2-12 (metformin)	-	-	[37]
Voglibose	Water (Taurine and Sodium periodate)	222nm	0.003 – 0.024	0.00263	0.0079	[38]
		235nm		0.00114	0.0034	
Metformin + voglibose	Methanol (Taurine and Sodium periodate)	220nm (metformin)	10-50 (metformin)	0.86 (metformin)	5.11 (metformin)	[39]
		242nm (Voglibose)	2-10 (Voglibose)	0.62 (Voglibose)	2.25 (Voglibose)	

LOQ: Limit of quantification; LOD: Limit of Detection

5. Chromatography Method

• High Performance Liquid Chromatography Method

- **HPLC as analytical method for miglitol and voglibose [40-44]:** Chromatography, in all of its variants, is frequently employed as a separating and analytical method. HPLC, which evolved from classical column chromatography, is currently one of the most important tools in analytical chemistry. The main and essential analytical instrument used in all phases of drug discovery, development, and production is HPLC. HPLC is the primary method for verifying the peak purity of new chemical entities, tracking reaction changes during scale-up or synthesis processes, evaluating new formulations, and performing quality control and assurance on completed pharmaceutical products.
- **Goal of HPLC:** Quantify the primary drug, all impurities from processes, all synthetic intermediates that are easily available, and any degradants.

- **Principle:** The stationary phase, or sample solution, is injected into a porous column, while the mobile phase, or liquid phase, is pumped through the column at a greater pressure. The separation principle employed is adsorption of solute on stationary phase based on its affinity for stationary phase. **Figure 4:** depicts HPLC instrumentation. HPLC of miglitol and voglibose are shown in Table No. 2

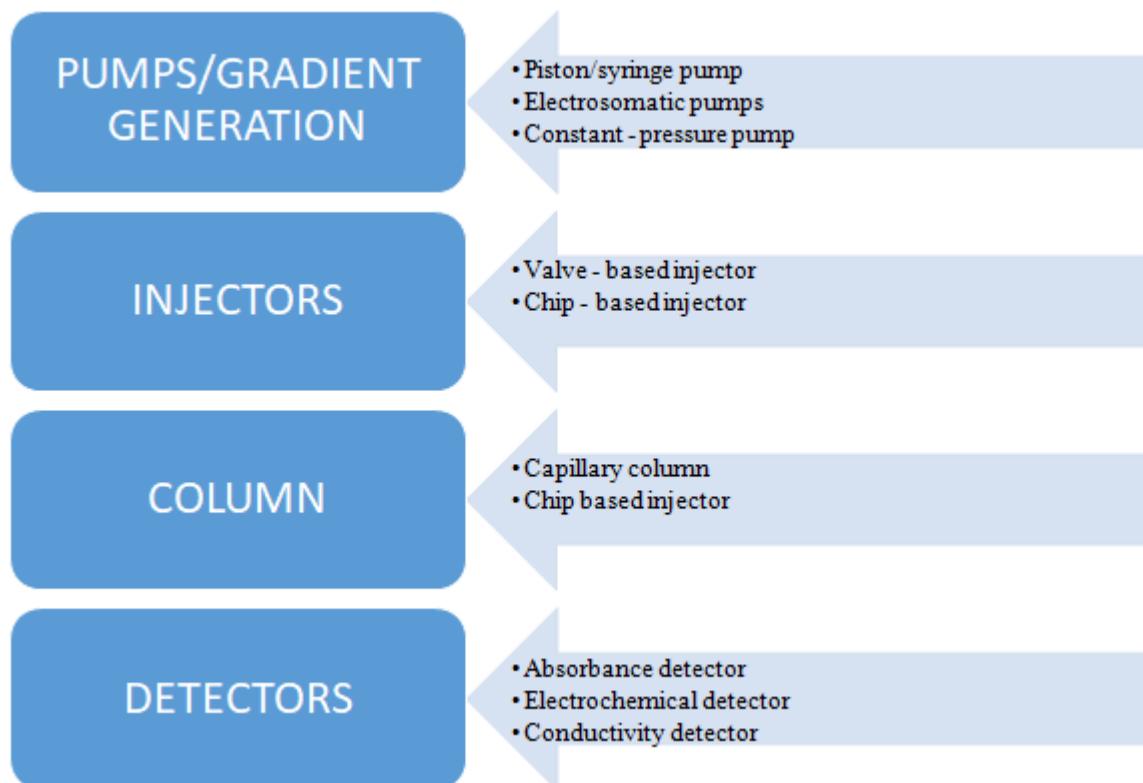


Figure 4: Instrumentation of HPLC

Table No. 2: HPLC of Miglitol and Voglibose

Drug	Detection	MP	SP	Linearity($\mu\text{g/ml}$)	LOD($\mu\text{g/ml}$)	LOQ($\mu\text{g/ml}$)	Ref
Metformin + voglibose + pioglitazone	232nm	0.1% v/v acetonitrile: triethylamine (30:70, v/v)	cosmosil C18withAutoc hro-3000 software	Metformin = 200-600	Metformin = 5.45	Metformin = 16.52	[45]
				Voglibose=0.08-0.24	Voglibose = 0.0032	Voglibose = 0.0097	
				Pioglitazone = 30-90	Pioglitazon = 0.93	Pioglitazone = 2.83	
Voglibose	282nm	potassium dihydrogen phosphate: acetonitrile: methanol	-	100 to 500	30	100	[46]
Repaglinide and voglibose	255nm	Methanol and dihydrogen phosphate buffer	-	2-18	Repaglinide = 0.18 Voglibose = 0.52	Repaglinide = 0.32 Voglibose = 0.87	[47]
Metformin + voglibose + glimepiride	230nm	solution A 0.02 M Phosphate buffer solution B Diluent: Water: acetonitrile (50:50).	Inertsil ODS 3Vcolumn	Metformin=200-600	Metformin = 0.05	Metformin = 1.5	[48]
				Voglibose= 0.08-0.24	Voglibose= 0.004	Voglibose= 0.012	
				Glimepiride = 0.8-2.4	Glimepiride = 0.002	Glimepiride = 0.006	
Miglitol	-	Acetonitrile and 0.02M Phosphate buffer	-	Linear relationship with r^2 found to be >0.9987	0.3	0.98	[49]
Miglitol	210nm	Phosphoric acid and acetonitrile buffer	-	Linear relationship with r^2 found to be 0.999	-	-	[50]

Miglitol	220nm	Acetonitrile and monobasic sodium phosphate	-	Linear relationship with $r^2 = 0.9986$	5.8	18.7	[51]
Miglitol	216nm	0.05M ammonium acetate	-	Linear relationship with $r^2 = 0.996$	20	70	[52]
Miglitol	-	Sodium 1-octanesulfonate as an ion-pair reagent	-	10 – 2500	-	-	[53]
Miglitol+ Metformin	236nm	Water: methanol	-	2.5 to 7.5 (miglitol) 25 to 75 for (metformin)	0.6607 (miglitol) 1.740 (metformin)	2.0021 (miglitol) 5.2736 (metformin)	[54]
Miglitol + metformin	238nm	Phosphate buffer and methanol	-	200-500 (miglitol) 20-50 (metformin)	100(miglitol) 30(metformin)	0.82 (miglitol) 0.25(metformin)	[55]
Miglitol	270nm	phosphate buffer-methanol	-	Linear relationship with $r^2 = 0.9999$	0.05	0.15	[56]
Voglibose	-	Acetonitrile and water (50:50)	C18column	10- 100	2.91	9.7	[57]
Voglibose	-	Acetonitrile: water (20:80 v/v)	Agilent TCC18 5 μ m column	10-70	0.037	0.114	[58]
Voglibose	-	Acetonitrile: water (70:30 v/v)	C18 column	10-60	0.054	0.16	[59]
Voglibose + metformin	-	0.02M KH ₂ PO ₄ : ACN (50:50 v/v)	Hypersil BDS C18 column	Voglibose= 0.3-0.18 Metformin = 50-300	-	-	[60]

Voglibose + metformin	-	ACN:Buffer pH - 6.5 (62:38 v/v)	C18:250X4.6m m, 5 μ , amino SS Column	Voglibose= 0.30-0.90	-	-	[61]
				Metformin = 500-1500			
Voglibose + metformin	-	Buffer: ACN (380:620)	C18:250X4.6m m, 5 μ , amino SS Column	Voglibose= 0.30-0.90	-	-	[62]
				Metformin = 500-1500			
Voglibose + metformin	-	Phosphate Buffer: ACN = 65: 35	Waters ODS (C18) RP Column	Voglibose= 10-60	Voglibose= 0.06	Voglibose= 0.18	[63]
				Metformin = 5-40	Metformin = 0.08	Metformin = 0.24	
Voglibose + repaglinide	-	KH ₂ PO ₄ Buffer, pH 3.5: Methanol (30:70% v/v)	Waters ODS (C18) RP Column	Repaglinide = 7.5 - 22.5	Repaglinide = 0.541	Repaglinide = 1.639	[64]
				Voglibose= 4.5 - 13.5	Voglibose= 0.38	Voglibose= 1.171	

LOQ: Limit of quantification; LOD: Limit of Detection; SP: Solid phase; MP: Mobile phase

- **Ultra Performance Liquid Chromatography Method**

- **UPLC As Analytical Method For Miglitol And Voglibose [65]:** Modern techniques such as UPLC give liquid chromatography a new lease on life. UPLC, or ultra performance liquid chromatography, is a technology that increases in three areas: "speed, resolution, and sensitivity." UPLC is superior than HPLC for particles with diameters smaller than 2 m and can achieve greater resolution, speed, and sensitivity. Analytical laboratories are not immune to this trend, as UPLC analysis now yields higher-quality data. Separation and quantification in UPLC are performed at extremely high pressures (up to 100M Pa).UPLC of miglitol and voglibose are shown in Table No. 3.

Table No. 3: UPLC of miglitol and voglibose

Drug	SP	MP	Linearity (µg/ml)	LOD (µg/ml)	LOQ(µg/ml)	Ref.
Miglitol		Acetonitrile and ammonium acetate with formic acid.	150–4000	-	150	[66]
Metformin + Voglibose + glimepiride	Inertsil ODS	Buffer (pH 3.0): Methanol (70:30v/v).	Metformin = 300 – 700	Metformin = 2.98	Metformin = 9.97	[67]
			Glimepiride = 0.6-1.4	Glimepiride = 2.95 µg/ml	Glimepiride = 9.97	
			Voglibose= 0.12-0.28	Voglibose= 2.97	Voglibose= 9.98	

LOQ: Limit of quantification; LOD: Limit of Detection; SP: Solid phase; MP: Mobile phase

6. Hyphenated Techniques

- **Hyphenated techniques as analytical method for miglitol and voglibose [68]:** The hyphenated techniques are created by combining two or three techniques in order to enhance analytical methods' capabilities and widen their applications. Table 4 shows hyphenated method of miglitol and voglibose.
- **LC/MS:** Over the past ten years, the use of high-performance liquid chromatography and mass spectrometry (LC/MS) has significantly impacted drug development. Techniques based on liquid chromatography/mass spectrometry (LC/MS) offer special possibilities for pharmaceutical analysis. Sensitivity, selectivity, speed of analysis, and cost effectiveness are just a few of the outstanding analytical methods of merit that make LC/MS procedures useful for a wide range of pharmaceutically relevant substances. These analytical functions have continuously advanced, making instruments more user-friendly and trustworthy. These advancements came at the right time and corresponded with the previously mentioned developments in the pharmaceutical industry. There are four technical factors that have been crucial for the recent acceptance of LC/MS-based procedures in the pharmaceutical business, together with time and perception difficulties.

- Sciences of separation
- Mass spectrometry
- Information
- Widened scope of application

Table No. 4: Hyphenated techniques of miglitol and voglibose

Drug	Methods	SP	MP	Linearity($\mu\text{g/ml}$)	LOD($\mu\text{g/ml}$)	LOQ($\mu\text{g/ml}$)	Ref.
Miglitol	LC-MS	-	Ammonium acetate	Good linearity with $r^2 \geq 0.9986$	1	5	[69]
Miglitol	LC-MS	-	Ammonium acetate and acetonitrile - methanol	Linear relationship with $r^2 = \geq 0.9984$	-	0.5	[70]
Miglitol + metformin	LC-MS	-	Ammonium acetate and miglitol	25–4000 (Miglitol) 20–2000 (Metformin)	7.08 (Miglitol) 3.83 (Metformin)	22.91 (Miglitol) 10.82 (Metformin)	[71]
Voglibose	LC-MS	Waters X Terra MS C15 μm column	solution A = formic acid in water and solution B = formic acid in methanol (50:50)	25.0-1200	1.5	3.0	[72]
Voglibose	LC-VD	Novapak C18 column	Buffer (0.01M mixture of sodium dihydrogen orthophosphate and disodium hydrogen orthophosphate) and acetonitrile (35:65 v/v)	LC-VD – 20–30	-	-	[73]

	LC-MS	Venusil XBPPH column	0.01% formic acid and methanol (95:5 v/v)				
Voglibose	LC-FD	Cosmosil® 5NH2-MS column	Acetonitrile and NaH ₂ PO ₄ (2:1 v/v)	50–1000.	9.4	29	[74]
	LC-MS		10mM aqueous NH ₄ OAc and acetonitrile (3:7v/v)		18	52	

LOQ: Limit of quantification; LOD: Limit of Detection; SP: Solid phase; MP: Mobile phase

II. CONCLUSION

This overview discusses on the importance of diabetes mellitus as a metabolic disorder that affects protein, lipid, and carbohydrate metabolism as a result of problems with insulin secretion or action. They concentrate particularly on T2DM and the use of alpha-glucosidase inhibitors, such as miglitol and voglibose, as therapy alternatives to manage T2DM by decreasing postprandial blood glucose levels by delaying the absorption of carbohydrates. This study has highlighted the value of developing and validating analytical methods in pharmaceutical research. The identification, classification, and determination of drug compounds and products, including miglitol and voglibose, has been discussed using a variety of analytical techniques, including UV-Visible spectroscopy, high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), and hyphenated techniques like LC-MS. The overview emphasizes the need for proper validation of analytical methods to ensure their suitability and safety for specific purposes. Parameters recommended by regulatory agencies like FDA, USP, and ICH are mentioned for conducting method validation effectively. Overall, a comprehensive overview of the analytical methods and validation techniques used for miglitol and voglibose, which are crucial in pharmaceutical research and development has been provided. The information presented here can serve as a valuable reference for researchers and scientists working in the field of diabetes mellitus and anti-diabetic drug development.

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