**Analytical Methods and Validation of Miglitol and Voglibose: An Overview**

Smita Suthar, Dipti Pal, Aman Naskar, Sanmati K Jain\*

Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.), India

E-mail address: sanmatijain72@yahoo.co.in (S.K. Jain); ORCID ID: 0000-0002-4798-7151

 **ABSTRACT**

Diabetes mellitus (DM) is a metabolic disorder that affects protein, lipid, and carbohydrate metabolism and is brought on by issues with insulin secretion or action. Severe diabetes side effects such retinopathy, neuropathy, nephropathy, cardiovascular issues, and ulceration can develop as the illness worsens. Type 1 (T1DM) and Type 2 (T2DM), the two main kinds, have different pathogenic characteristics. T1DM is characterised by a failure to produce enough insulin as a result 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 slow down the absorption of carbohydrates, which lowers 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

**I. INTRODUCTION**

**A. Diabetes Mellitus**

The metabolic illness known as diabetes mellitus (DM) is brought on by a problem with insulin secretion, action, or both. Chronic hyperglycaemia brought on by an insulin shortage also causes problems with protein, lipid, and carbohydrate metabolism. As the condition worsens, tissue or vascular damage occurs, which can cause serious diabetic side effects such retinopathy, neuropathy, nephropathy, cardiovascular problems, and ulceration[1]. Although the two basic etiopathogenetic categories of type 1 and type 2 DM account for the majority of instances of diabetes, this rigorous classification may not be appropriate in all circumstances [2].

Type 1 diabetes mellitus (T1DM), commonly referred to as autoimmune diabetes, is a chronic condition that causes hyperglycaemia due to an inability to produce enough insulin as a result of the death of pancreatic beta cells [3,4].

The major abnormalities in T2DM continue to be insulin resistance and decreased insulin secretion. Due to hyperglycaemia and certain elements of the insulin resistance (metabolic) syndrome, people with T2DM are at a significant risk for both microvascular consequences (such as retinopathy, nephropathy, and neuropathy) and macrovascular complications (such as cardiovascular comorbidities) [5,6,7].

Anti-diabetic medications come in a variety of classes, and the choice of one relies on the type of diabetes, the patient's age and circumstances, among other things. Treatment options include substances that improve the pancreas' production of insulin, raise the sensitivity of the target organs to insulin, and slow down the absorption of glucose from the gastrointestinal tract [8,9,10].

Oral hypoglycaemic agents include thiazolidinediones, biguanides, alpha glucosidase, DPP‐IV inhibitors etc for treatment of T2DM [11,12,13,14,15,16].

**B. Alpha glucosidase inhibitor**

 A class of anti-diabetic medications 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 a-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, 18, 19, 20, 21].

**1. 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. With a tiny initial dose that is gradually increased as tolerated, the incidence of digestive issues may be decreased [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, cardiovascular, respiratory, or haematological indicators [23].

**2. 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, the majority 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].

**C. Analytical Method Development and Validation**

**1. Analytical method development**

The discovery, development, and production of pharmaceuticals depend heavily on the development and validation of analytical methods [26]. To compare a defined characteristic of the drug substance or drug products to predetermined acceptance criteria for that characteristic, an analytical technique is designed [27]. Spectral, chromatographic, electrochemical, hyphenated, or other analytical methods are all possible. Development of analytical methods is the process of choosing an exact assay method to ascertain a formulation's composition [28].

**Figure 1: General analytical methods**

**Purpose of analytical method development**

The identification, classification, and determination of pharmaceuticals in combinations such dosage forms and biological fluids are revealed by drug analysis. The primary goal of analytical methods used in the manufacturing process and drug development is to provide information about potency (which can be directly related to the need for a known dose), impurity (related to the safety profile of the drug), bioavailability (which includes important drug characteristics like crystal form, drug uniformity, and drug release), stability (which indicates the degradation products), and effect of manufacturing parameters to ensure that the product is as safe as possible [29].

**Steps of analytical 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].

**2. Validation**

The goal of validating an analytical method is to show that it is appropriate for the purpose for which it is being used [31].

Typical validation parameters recommended by FDA, USP, and ICH are as follows:

**Figure 3: Validation parameters**

**B. SPECTROPHOTOMETRIC METHOD**

**UV-Visible spectroscopy as analytical method for miglitol and voglibose [32, 33, 34].**

As a spectrophotometric technique, UV-VIS spectroscopy is used to measure the intensity of light in the UV (10-400 nm) and VIS (400-800 nm) areas as a function of wavelength. It is regarded as the oldest analytical technique. The amount of radiation absorbed by the analyte is measured after the analyte absorbs light of a particular wavelength (UV and VIS only). The interaction of UV-VIS EMR with the analyte produces the spectrum after UV-VIS light has been absorbed.

**Principle**

Based on the phenomena of light absorption, UV-VIS spectroscopy measures the concentration of analytes in a sample solution by measuring the amount of absorbed light. Absorption increases as analyte concentration increases.

**Electronic Transitions**

The stimulation of valence electrons from the ground state to the excited state is connected to the absorption of electronic energy levels (UV-VIS radiations) by an organic molecule. Electronic transitions typically take place from the excited state, which has the highest molecular orbital, after energy absorption.

 **Types of Electronic Transitions**

1**.** σ - σ\* Electronic Transition

2. pi - pi\* Electronic Transition

3. n - σ\* Electronic Transition

4. n - pi\* Electronic Transition

**Components of UV-VIS Spectrophotometer**

**Figure 4: Components of UV-VIS Spectrophotometer**

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

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

 LOD: Limit of Detection; LOQ: Limit of quantitation

**C. CHROMATOGRAPHY METHOD**

**1. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY METHOD**

**HPLC as analytical method for miglitol and voglibose [40, 41, 42, 43, 44].**

Chromatography, in all of its variants, is frequently employed as a separating and analytical method.

One of the most crucial tools in analytical chemistry nowadays is High Performance Liquid Chromatography (HPLC), which was developed from the traditional column chromatography. The main and essential analytical instrument used in all phases of drug discovery, development, and production is high-performance liquid chromatography (HPLC). The preferred approach for testing the peak purity of new chemical entities, keeping track of reaction changes during scale-up or synthesis processes, assessing new formulations, and performing quality control and assurance on finished pharmaceutical products is HPLC.

**Goal of HPLC**

Quantify the primary drug, all contaminants from reactions, all readily available synthetic intermediates, and any degradants.

**Principle**

The stationary phase, or sample solution, is injected into a porous column, and the mobile phase, or liquid phase, is pumped through the column at a higher pressure. The adsorption of solute on stationary phase based on its affinity towards stationary phase is the separation principle that is used.

The technique of HPLC has following features.

* High resolution
* Small diameter, Stainless steel, Glass column
* Rapid analysis
* Relatively higher mobile phase pressure
* Controlled flow rate of mobile phase

**Instrumentation**

**Figure 5: Instrumentation of HPLC**

**Table No. 2: HPLC of miglitol and voglibose**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Detection** | **MP** | **SP** | **Linearity** | **LOD** | **LOQ** | **Ref** |
| Metformin + voglibose + pioglitazone | 232nm | 0.1% v/vacetonitrile:triethylamine(30:70, v/v) | cosmosil C18(4.6×250mm,5μm) withAutochro-3000 software | Metformin - 200-600 μg/ml | Metformin- 5.45μg/ml | Metformin- 16.52μg/ml | [45] |
| Voglibose - 0.08-0.24 μg/ml | Voglibose- 0.0032μg/ml | Voglibose- 0.0097μg/ml |
| Pioglitazone - 30-90 μg/ml | Pioglitazone- 0.93μg/ml | Pioglitazone- 2.83μg/ml |
| Voglibose | 282nm | potassium dihydrogen phosphate: acetonitrile : methanol |  | 100 to 500 ng/ml | 30ng/ml | 100ng/ml | [46] |
| Repaglinide and voglibose | 255nm | Methanol and dihydrogen phosphate buffer |  | 2-18 μg/ml | Repaglinide- 0.18 μg/mlVoglibose- 0.52 μg/ml | Repaglinide- 0.32 μg/mlVoglibose- 0.87 μg/ml | [47] |
| Metformin + voglibose + glimepiride | 230nm | **solution A**0.02 M Phosphate bufferadjusted to pH 2.5 usingdilute orthophosphoricacid**solution B**Diluent: Water:acetonitrile (50:50). | Inertsil ODS 3V(150 × 4.6 mm,i.e. 5 μm)column | Metformin - 200-600 μg/ml | Metformin - 0.05 μg/ml | Metformin -1.5 μg/ml, | [48] |
| Voglibose - 0.08-0.24 μg/ml | Voglibose -0.004 μg/ml | Voglibose - 0.012 μg/ml |
| Glimepiride - 0.8 - 2.4 μg/ml | Glimepiride - 0.002 μg/ml | Glimepiride - 0.006 μg/ml |
| Miglitol | - | Acetonitrile and 0.02M Phosphate buffer |  | Linear relationship with r2 found to be >0.9987 | 0.3μg/ml | 0.98μg/ml | [49] |
| Miglitol | 210nm | Phosphoric acid and acetonitrile buffer |  | Linear relationship with r2 found to be 0.999 | 0.02% (*w/w*) | 0.05% (*w/w*) | [50] |
| Miglitol | 220nm | Acetonitrile and monobasic sodium phosphate |  | Linear relationship with r2 = 0.9986 | 5.8ng/ml | 18.7ng/ml | [51] |
| Miglitol | 216nm | 0.05M ammonium acetate | - | Linear relationship with r2 = 0.996 | 20 μg/ml | 70 μg/ml | [52] |
| Miglitol | - | Sodium1-octanesulfonate as an ion-pair reagent |  | 10 – 2500ngl/ml | - | - | [53] |
| Miglitol+ Metformin | 236nm | Water: methanol |  | 2.5 to 7.5 μg/ml for Miglitol25 to 75 μg/ml for Metformin | Miglitol- 0.6607 μg/mlMetformin- 1.740 μg/ml | Miglitol- 2.0021 μg/mlMetformin- 5.2736 μg/ml | [54] |
| Miglitol + metformin | 238nm | Phosphate buffer and methanol |  | 200-500μg/ml (miglitol)20-50μg/ml (metformin) | Metformin - 30ng/ml Miglitol - 100ng/ml | Metformin - 0.25μg/mlMiglitol - 0.82 μg/ml. | [55] |
| Miglitol | 270nm | phosphate buffer- methanol |  | Linear relationship with r2 = 0.9999 | 0.05 µg/ml | 0.15 µg/ml | [56] |
| Voglibose | - | Acetonitrile and water (50:50) | C18(250 x 4.6 mm, 5 μm) column | 10‐100 µg/ml | 2.91 µg/ml | 9.7 µg/ml | [57] |
| Voglibose | - | Acetonitrile: water (20:80 v/*v*) | Agilent TC C18(250 × 4.6 mm) 5μm column | 10-70 µg/ml | 0.037 µg/ml | 0.114 µg/ml | [58] |
| Voglibose | - | Acetonitrile: water (70:30 v/v) | C18 column(250 mm x 4.6 mm, 5 μm) | 10-60 µg/ml | 0.054 µg/ml | 0.16 µg/ml | [59] |
| Voglibose + metformin | - | 0.02M KH2PO4: ACN(50:50 v/v) | Hypersil BDSC18 column(250×4.6, 5 μm) | Voglibose - 0.3-0.18 µg/ml |  | - | [60] |
| Metformin - 50-300 µg/ml |
| Voglibose + metformin | - | ACN: buffer pH - 6.5(62:38 v/v) | C18:250X4.6mm, 5μ, amino SSColumn | Voglibose - 0.30-0.90 µg/ml |  | - | [61] |
| Metformin - 500-1500 µg/ml |
| Voglibose + metformin | - | Buffer: ACN (380:620) | C18:250X4.6mm, 5μ,amino SSColumn | Voglibose - 0.30-0.90 µg/ml |  | - | [62] |
| Metformin - 500-1500 µg/ml |
| Voglibose + metformin | - | Phosphate Buffer (pH--6.5): -ACN = 65 : 35 | Waters ODS(C18) RPColumn, 250mm x 4.6 mm | Voglibose - 10-60 µg/ml | Voglibose - 0.06 µg/ml | Voglibose - 0.18 µg/ml | [63] |
| Metformin - 5-40 µg/ml | Metformin - 0.08 µg/ml | Metformin - 0.24 µg/ml |
| Voglibose + repaglinide | - | KH2PO4 Buffer, pH 3.5:Methanol (30:70%v/v) | Waters ODS(C18) RPColumn, 250mm x 4.6 mm | Repaglinide - 7.5 - 22.5 µg/ml | Repaglinide - 0.541 µg/ml | Repaglinide - 1.639 µg/ml | [64] |
| Voglibose - 4.5 - 13.5 | Voglibose - 0.38 | Voglibose - 1.171 |

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

**2. ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY METHOD**

**UPLC as analytical method for miglitol and voglibose [65].**

Modern techniques like UPLC give liquid chromatography a fresh new look. Ultra performance liquid chromatography, or UPLC, is a technique that improves primarily in three areas: "speed, resolution, and sensitivity. Compared to high-performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC) is appropriate for particles with a diameter of less than 2 m and can achieve superior resolution, speed, and sensitivity. Analytical laboratories are not an exception to this trend as UPLC analysis now results in better-quality goods. In UPLC, the separation and quantification are carried out at extremely high pressures (up to 100M Pa).

**Table No. 3: UPLC of miglitol and voglibose**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **SP** | **MP** | **Linearity** | **LOD** | **LOQ** | **Ref.** |
| Miglitol |  | Acetonitrile and ammonium acetate with formic acid. | 150–4000 ng/mL, | - | 150 ng/mL | [66] |
| Metformin + Voglibose + glimepiride | InertsilODS (50x 1.7mm,3μm,) | Buffer (pH3.0):Methanol(70:30v/v). | Metformin – 300 – 700 µg/ml | Metformin - 2.98 µg/ml | Metformin - 9.97 µg/ml | [67] |
| Glimepiride - 0.6-1.4 µg/ml | Glimepiride - 2.95 µg/ml | Glimepiride -9.97 µg/ml |
| Voglibose - 0.12-0.28 µg/ml | Voglibose - 2.97 µg/ml | Voglibose - 9.98 µg/ml |

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

**D. HYPHENATED TECHNIQUES**

**Hyphenated techniques as analytical method for miglitol and voglibose [68].**

 **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.

1. Sciences of separation

2. Mass spectrometry

3. Information

4. Widened scope of application

**Table No. 4: Hyphenated techniques of miglitol and voglibose**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Methods** | **SP** | **MP** | **Linearity** | **LOD** | **LOQ** | **Ref.** |
| Miglitol | LC-MS | - | Ammonium acetate | Good linearity with r2 ≥ 0.9986 | 1ng/ml | 5ng/ml | [69] |
| Miglitol | LC-MS | - | Ammonium acetate and acetonitrile - methanol | Linear relationship with r2 = ≥ 0.9984 | - | 0.5ng/ml | [70] |
| Miglitol + metformin | LC-MS | - | Ammonium acetate and miglitol | 20–2000 ng/mL for Metformin 25–4000 ng/mL for Miglitol | Miglitol – 7.08 ng/mlMetformin – 3.83ng/ml | Miglitol- 22.91ng/mlMetformin- 10.82 ng/ml | [71] |
| Voglibose | LC-MS | Waters X Terra MS C18,100 mmx2.1id, 5 **μ**m column | **solution A** (1 mL of formic acid in 1000 mL ofwater) and **solution B** (1 mL of formic acid in 1000 mL ofmethanol)in the ratio of 50:50 | 25.0-1200 hg/mL | 1.5 hg/mL | 3.0 hg/mL. | [72] |
| Voglibose | LC-VD | NovapakC18(300×3.9mm, 4μm)column | Buffer (0.01M mixture of sodiumdi hydrogen orthophosphate anddisodium hydrogenorthophosphate, pH 6.0) andacetonitrile in 35:65 v/v ratio | LC-VD – 20 –30 µg/ml | - | - | [73] |
| LC-MS | VenusilXBPPH(150×4.6mm, 5μm)column | 95:5 v/vmixtureof 0.01%formic acid andmethanol |
| Voglibose | LC-FD | Cosmosil® 5NH2-MScolumn(150mm×4.6 mm,5μm) | Acetonitrile and 30mM NaH2PO4(pH 6.5) (2:1, v/v) | 50–1000 ng/ml. | 9.4 ng/ml | 29 ng/ml | [74] |
| LC-MS | 10mM aqueousNH4OAcand acetonitrile(3:7, v/v) | 18 ng/ml | 52 ng/ml |

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

**E. CONCLUSION**

This overview discuss 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 Type 2 diabetes mellitus (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.

**F. REFERENCES**

1. S. Bastaki, “Diabetes Mellitus And Its Treatment,” Dubai Diabetes And Endocrinology Journal, 13(3), 2005, Pp. 111-134. [Https://Doi.Org/10.1159/000497580](https://doi.org/10.1159/000497580)
2. U. Alam, O. Asghar, S. Azmi, & R. A. Malik, “General Aspects Of Diabetes Mellitus,” Handbook Of Clinical Neurology, 126, 2014, Pp. 211-222.[Https://Doi.Org/10.1016/B978-0-444-53480-4.00015-1](https://doi.org/10.1016/B978-0-444-53480-4.00015-1)
3. A. Katsarou, S. Gudbjörnsdottir, A. Rawshani, D. Dabelea, E. Bonifacio, B. J. Anderson, Et Al., “Type 1 Diabetes Mellitus,” Nature Reviews Disease Primers, 3(1), 2017, Pp. 1-17. Https://Doi.Org/10.1038/Nrdp.2017.16
4. L. Eiselein, H. J. Schwartz, & J. C. Rutledge, “The Challenge Of Type 1 Diabetes Mellitus,” Ilar Journal, 45(3), 2004, Pp. 231-236. [Https://Doi.Org/10.1093/Ilar.45.3.231](https://doi.org/10.1093/ilar.45.3.231)
5. R. A. Defronzo, E. Ferrannini, L. Groop, R. R. W. H. Henry, Et Al., “Type 2 Diabetes Mellitus,” Nature Reviews Disease Primers, 1(1), 2015, Pp. 1-22. [Https://Doi.Org/10.1038/Nrdp.2015.19](https://doi.org/10.1038/nrdp.2015.19)
6. A. B. Olokoba, O. A. Obateru, & L. B. Olokoba, “Type 2 Diabetes Mellitus: A Review Of Current Trends,” Oman Medical Journal, 27(4), 2012, Pp. 269. Doi: [10.5001/Omj.2012.68](https://doi.org/10.5001/omj.2012.68)
7. J. L. Leahy, “Pathogenesis Of Type 2 Diabetes Mellitus” Archives Of Medical Research, 36(3), 2005, Pp. 197-209. [Https://Doi.Org/10.1016/J.Arcmed.2005.01.003](https://doi.org/10.1016/j.arcmed.2005.01.003)
8. P. B. Mane, R. V. Antre, & R. J. Oswal, “Antidiabetic Drugs: An Overview,” Int. J. Pharm. Chem. Sci, 1(1), 2012, Pp. 301-6.
9. L. H. Bosenberg, And Danie Gerhardus Van Zyl, "The Mechanism Of Action Of Oral Antidiabetic Drugs: A Review Of Recent Literature." Journal Of Endocrinology, Metabolism And Diabetes In South Africa 13, No. 3 2008, Pp. 80-88.
10. B. Lorenzati, C. Zucco, S. Miglietta, F. Lamberti, & G, “Bruno Oral Hypoglycemic Drugs: Pathophysiological Basis Of Their Mechanism Of Action,” Pharmaceuticals, 3(9), 2010, Pp. 3005-3020. [Https://Doi.Org/10.3390/Ph3093005](https://doi.org/10.3390/ph3093005)
11. 11 C. Day, "Thiazolidinediones: A New Class Of Antidiabetic Drugs." Diabetic Medicine 16, No. 3, 1999, Pp. 179-192. [Https://Doi.Org/10.1046/J.1464-5491.1999.00023.X](https://doi.org/10.1046/j.1464-5491.1999.00023.x)
12. I. Idris, & R. Donnelly, “Dipeptidyl Peptidase‐Iv Inhibitors: A Major New Class Of Oral Antidiabetic Drug,” Diabetes, Obesity And Metabolism, 9(2), 2007, Pp. 153-165. [Https://Doi.Org/10.1111/J.1463-1326.2007.00705.X](https://doi.org/10.1111/j.1463-1326.2007.00705.x)
13. G. Schäfer, “Biguanides,” A Review Of History, Pharmacodynamics And Therapy. Diabete & Metabolisme, 9(2), 1983, Pp. 148-163.
14. R. K. Campbell, J. R. White Jr, & B. A. Saulie, “Metformin: A New Oral Biguanide,” Clinical Therapeutics, 18(3), 1996, Pp. 360-371. [Https://Doi.Org/10.1016/S0149-2918(96)80017-8](https://doi.org/10.1016/S0149-2918%2896%2980017-8)
15. O. Mehrpour, F. Saeedi, C. Hoyte, A. Hadianfar, S. Nakhaee, & J. Brent, “Distinguishing Characteristics Of Exposure To Biguanide And Sulfonylurea Anti-Diabetic Medications In The United States,”  The American Journal Of Emergency Medicine, 56, 2022, Pp. 171-177. [Https://Doi.Org/10.1016/J.Ajem.2022.03.023](https://doi.org/10.1016/j.ajem.2022.03.023)
16. S. Kalra, “Alpha Glucosidase Inhibitors,” Jpma. The Journal Of The Pakistan Medical Association, 64(4), 2014, Pp. 474-476.
17. M. Akmal, & R. Wadhwa, “Alpha Glucosidase Inhibitors”, 2020.
18. F. A.Van De Laar, P. L. Lucassen, R. P. Akkermans, E. H. Van De Lisdonk, G. E. Rutten, & C. Van Weel, “Alpha‐Glucosidase Inhibitors For Type 2 Diabetes Mellitus,” Cochrane Database Of Systematic Reviews, (2), 2005.
19. H. Bischoff, “The Mechanism Of Alpha-Glucosidase Inhibition In The Management Of Diabetes,” Clinical And Investigative Medicine. Medecine Clinique Et Experimentale, 18(4), 1995, Pp. 303-311.
20. M. S. Hedrington, & S. N. Davis, “Considerations When Using Alpha-Glucosidase Inhibitors In The Treatment Of Type 2 Diabetes,” Expert Opinion On Pharmacotherapy, 20(18), 2019, Pp. 2229-2235. [Https://Doi.Org/10.1080/14656566.2019.1672660](https://doi.org/10.1080/14656566.2019.1672660)
21. S. R. Joshi, E. Standl, N. Tong, P. Shah, S. Kalra, & R. Rathod, “Therapeutic Potential Of Α-Glucosidase Inhibitors In Type 2 Diabetes Mellitus: An Evidence-Based Review,” Expert Opinion On Pharmacotherapy, 16(13), 2015, 1959-1981. [10.1517/14656566.2015.1070827](https://doi.org/10.1517/14656566.2015.1070827)
22. L. Zhang, Q. Chen, L. Li, J. S. Kwong, P. Jia, P. Zhao, & X. Sun, “Alpha-Glucosidase Inhibitors And Hepatotoxicity In Type 2 Diabetes: A Systematic Review And Meta-Analysis,”  Scientific Reports, 6(1), 2016, 32649.Https://Doi.Org/10.1038/Srep32649
23. L. K. Campbell, D. E. Baker, & R. K. Campbell, “Miglitol: Assessment Of Its Role In The Treatment Of Patients With Diabetes Mellitus,” Annals Of Pharmacotherapy, 34(11), 2000, 1291-1301. [Https://Doi.Org/10.1345/Aph.19269](https://doi.org/10.1345/aph.19269)
24. L. J. Scott, & C. M. Spencer, “Miglitol: A Review Of Its Therapeutic Potential In Type 2 Diabetes Mellitus,” Drugs, 59(3), 2000, 521-549. [Https://Doi.Org/10.2165/00003495-200059030-00012](https://doi.org/10.2165/00003495-200059030-00012)
25. A. S. Dabhi, N. R. Bhatt, & M. J. Shah, “Voglibose: An Alpha Glucosidase Inhibitor,” Journal Of Clinical And Diagnostic Research: Jcdr, 7(12), 2013, 3023.[10.7860/Jcdr/2013/6373.3838](https://doi.org/10.7860/JCDR/2013/6373.3838)
26. K. Kaku, “Efficacy Of Voglibose In Type 2 Diabetes,” Expert Opinion On Pharmacotherapy, 15(8), 2014, 1181-1190. [Https://Doi.Org/10.1517/14656566.2014.918956](https://doi.org/10.1517/14656566.2014.918956)
27. J. Breaux, K. Jones, & P. Boulas, “Analytical Methods Development And Validation,” Pharm. Technol, 1, 2003, 6-13.
28. A. Procedures, “Methods Validation For Drugs And Biologics,” Guidance For Industry. Food And Drug Administration, 2015.
29. A. Chauhan, B. Harti Mittu P. Chauhan Analytical, “Method Development And Validation: A Concise Review,” J Anal Bioanal Tech, 6(233), 2015, 2. Doi: 10.4172/2155-9872.1000233
30. P. Ravisankar, C. N. Navya, D. Pravallika, & D. N. Sri, “A Review On Step-By-Step Analytical Method Validation,” Iosr J Pharm, 5(10), 2015, 7-19.
31. P. S. Singh, & G. Shah, “Analytical Method Development And Validation”  J Pharm Res2011, 4(5), 2011, 2330-2.
32. Chauhan, A. (2015). Harti Mittu B, Chauhan P (2015) Analytical Method Development And Validation: A Concise Review. J Anal Bioanal Tech, 6(233), 2. Doi: 10.4172/2155-9872.1000233
33. M. Picollo, M. Aceto, & T. Vitorino, “Uv-Vis Spectroscopy,” Physical Sciences Reviews, 4(4), 2018, 20180008.
34. H. Förster, “Uv/Vis Spectroscopy,” Characterization I: 2004, 337-426.
35. H. H. Perkampus, “Uv-Vis Spectroscopy And Its Applications,” Springer Science & Business Media, 2013.
36. N. M. Rao, J. Bagyalakshmi, & T. K. Ravi, “Development And Validation Of Uv-Spectroscopic Method For Estimation Of Voglibose In Bulk And Tablets,” J Chem Pharm Res, 2(2), 2010, 350-56.
37. F. A. Ibrahim, F. A. Ali, S. M. Ahmed, & M. M. Tolba, “Kinetic Determination Of Acarbose And Miglitol In Bulk And Pharmaceutical Formulations Using Alkaline Potassium Permanganate,” International Journal Of Biomedical Science: Ijbs, 3(1), 2007, 20.
38. S. R. Patel, P. V. Kabra, R. V. Kimbahune, R. Markad, & L. V. G Nargund, “Development And Validation Of Analytical Method For Quantitative Estimation Of Miglitol And Metformin In Combined Dosage Form,” Journal Of Applied Pharmaceutical Science, 2(7), 2012, 227-229.
39. T. B. Sadhana, K. M. Shrinivas, P. K. Supria, & K. R. Swapna, “Spectrophotometric Determination Of Voglibose In Bulk And Tablet Dosage Form By Absorption Maxima, First Order Derivative Spectroscopy And Area Under Curve Method,” Int J Pharm Res Dev, 5, 2013, 200-6.
40. H. D. Patel, J. Surati, Z. Dedania, S. M. Vijyendraswamy, “Simultaneous Estimation Of Voglibose And Metformin Hydrochloride In Tablet Dosage Form,” V-4, I-1, 2015
41. S. K. Bhardwaj, K. Dwivedia, & D. D. Agarwala, “A Review: Hplc Method Development And Validation" International Journal Of Analytical And Bioanalytical Chemistry, 5(4), 2015, 76-81.
42. P. K. Sahu, N. R. Ramisetti, T. Cecchi, S. Swain, C. S. Patro, & J. Panda, “An Overview Of Experimental Designs In Hplc Method Development And Validation,” Journal Of Pharmaceutical And Biomedical Analysis, 147, 2018, 590-611.
43. M. P. N. Patil, “Hplc Method Development–A Review,” Journal Of Pharmaceutical Research And Education, 1(2), 2017, 243-260.
44. R. J. Hamilton, & P. A. Sewell, “Introduction To High Performance Liquid Chromatography,” In Introduction To High Performance Liquid Chromatography,1982, Pp. 1-12.
45. K. B. Lynch, A. Chen, & S. Liu, “Miniaturized High-Performance Liquid Chromatography Instrumentation,” Talanta,  177, 2018, 94-103.
46. M. A. Shende, & B. R. Budde, “Novel Rp-Hplc Method Development And Validation For Simultaneous Estimation Of Metformin, Voglibose And Pioglitazone In Bulk And Triple Fixed Drug Combinations Pharmaceutical Dosage Form,” Journal Of Drug Delivery And Therapeutics, 9(1), 2019, 30-37.
47. N. M. Rao, K. R. Kumar, J. Bagyalakshmi, T. K. Ravi, & R. Mogili, “Rp-Hplc Method Development And Validation For Estimation Of Voglibose In Bulk And Tablet Dosage Forms,” Int. J. Res. Pharm. Sci, 1(2), 2010, 190-194.
48. T. K. R. Konatham, N. Vallakeerthi, & A. Masipogu, Method Development And Validation Of Repaglinide And Voglibose In Pure And Pharmaceutical Dosage Form By Using Reverse Phase High Performance Liquid Chromatography, 2020.
49. K. Neelima & Y. R. Prasad, “Analytical Method Development And Validation Of Metformin, Voglibose, Glimepiride In Bulk And Combined Tablet Dosage Form By Gradient Rp-Hplc,” Pharmaceut Meth, 5, 2014, 27-33.
50. S. M. Dhole, P. B. Khedekar, & N. D. Amnerkar, “Validated High Performance Liquid Chromatography Method For Determination Of Miglitol In Tablet Dosage Form,” Journal Of Pharmacy Research, 7(7), 2013, 595-599.
51. K. Balakumaran, M. Janagili, N. Rajana, S. Papureddy, & J. Anireddy, “Development And Validation Of Miglitol And Its Impurities By Rp-Hplc And Characterization Using Mass Spectrometry Techniques,” Scientia Pharmaceutica, 84(4), 2016, 654-671.
52. B. Shrivastava, U. S. Baghel, & M. Sahu, “Stability-Indicating Rp-Hplc Method For Estimation Of Miglitol In Bulk And Tablets. Indian Journal Of Pharmaceutical Sciences,” 72(6), 2010, 781.
53. N. C. & A. Jain, “New Rp-Hplc Method Of Miglitol In Tablet Dosage Form Including Forced Degradation Studies And Estimation In Spiked Rabbit Plasma,” Journal Of Young Pharmacists, 1(4), 2009, 285.
54. P. Nilam, P. Pinkal, & S. Khushbu, “Development And Validation Of Analytical Method For Simultaneous Estimation Of Miglitol And Metformin Hydrochloride In Tablet Dosage Form,” International Journal Of Pharmaceutical Sciences And Research, 5(11), 2014, 4820.
55. H. Asamoto, Y. Nobushi, T. Oi, & K. Uchikura, “Determination Of Miglitol By Column-Switching Ion-Pair Hplc With Tris (2, 2′-Bipyridine) Ruthenium (Ii)-Electrogenerated Chemiluminescence Detection,” Chemical And Pharmaceutical Bulletin, 63(6), 2015, 476-480.
56. Bhoomaiah, B., & Shree, A. J. (2014). Development And Validation Of Rp-Hplc Method For Simultaneous Determination Of Metformin And Miglitol In Bulk And Pharmaceutical Formulation. Int J Pharm Pharm Sci, 6(6), 135-41.
57. K. Basavaiah, & N. Rajendraprasad, “Development And Validation Of Novel Stability-Indicating High-Performance Liquid Chromatography Method For The Determination Of Miglitol In Pharmaceuticals,” The Thai Journal Of Pharmaceutical Sciences, 42(1), 2018, 37-34.
58. L. Karunanidhi, And R. Tirumala, “Determination Of Voglibose In Pharmaceutical Formulations By High Performance Liquid Chromatography Using Refractive Index Detection,” European Journal Of Chemistry 1 (4), 2010, 262‐265; Doi:10.5155/Eurjchem.1.4.262‐265.116
59. C. D. Shubhangi, G. W. Sanjay, And C.B. Mahendra, “Stability Indicating Rp-Hplc Method For Estimation Of Voglibose In Bulk And Tablet Dosage Form,” Pharmacophore 2013, Vol. 4 (5), 158-165,”
60. S. Y. Royal Debnath, Manjunath And T. Hemant Kumar, “Development And Validation Of New Rp-Hplc Method For The Estimation Of Voglibose In Bulk And Pharmaceutical Dosage Form,” International Journal Of Biomedical Research, 11(10), 2020. Doi: [Https://Doi.Org/10.7439/Ijbr](https://doi.org/10.7439/ijbr)
61. M. Gayathri Devi Et Al. “Analytical Method Development And Validation For The Estimation Of Metformin And Voglibose In Bulk And Fixed Dose Combination (Tablets) By Rp-Hplc,” Indo Am. J. P. Sci, 05(02), 2018.
62. K. Sonia And K. Prasad Babu, “Rp-Hplc Analysis Of Metformin Hydrochloride And Voglibose And Study Of Its Different Analytical Parameter,” Ijpsr, Vol. 4(4), 2013, 1469 1474.
63. M.S.Harikrishnan, D.Babu Ananth, “Estimation Of Metformin Hydrochloride And Voglibose In Tablet Dosage Form By Rp-Hplc Method," April 2016.
64. B. Mamatha Et Al. “Method Development, Validation And Forced Degradation Studies Of Voglibose And Metformin In Pure And Pharmaceutical Dosage Form By Rp-Hplc,” Ijpbs, 9 (4), 2019, 29-40. Doi: [Https://Doi.Org/10.21276/Ijpbs.2019.9.4.4](https://doi.org/10.21276/ijpbs.2019.9.4.4)
65. A. M. Patel, V. Kotadiya1, N. Tiwari1, P. Patani, “Development And Validation Of Stability Indicating Rp- Hplc Method For Simultaneous Estimation Of Repaglinide And Voglibose In Its Tablet Dosage Form,” Jetir, Volume 8, Issue 5, May 2021.
66. M. Taleuzzaman, S. Ali, S. J. Gilani, S. S. Imam, & A. Hafeez, “Ultra Performance Liquid Chromatography (Uplc)-A Review,” Austin J Anal Pharm Chem, 2(6), 2015, 1056.
67. R. Jain, O. Lukram, & A. Dwivedi, “Ultra‐Performance Liquid Chromatography Electrospray Ionization–Tandem Mass Spectrometry Method For The Estimation Of Miglitol In Human Plasma Using Metformin As The Internal Standard,”  Drug Testing And Analysis, 3(4), 2011, 255-262.
68. V. N. Kadam Et Al, “Development And Validation Of Analytical Methods For Simultaneous Estimation Of Voglibose, Glimepiride And Metformin Hydrochloride In Bulk And Tablet Dosage Form By Hplc,” Ijppr.Human, Vol. 1(2), 2014, 10-2.
69. M. S. Lee, & E. H. Kerns, “Lc/Ms Applications In Drug Development,” Mass Spectrometry Reviews, 18(3‐4), 1999, 187-279.
70. X. Li, Y. Wang, J. Wang, J. P. Fawcett, L. Zhao, & J. Gu, “Determination Of Miglitol In Human Plasma By Liquid Chromatography/Tandem Mass Spectrometry,” Rapid Communications In Mass Spectrometry: An International Journal Devoted To The Rapid Dissemination Of Up‐To‐The‐Minute Research In Mass Spectrometry, 21(2), 2007, 247-251.
71. A. Mizuno‐Yasuhira, K. Kinoshita, S. Jingu, & J. I. Yamaguchi, “A Sensitive And Selective Method For The Quantitative Analysis Of Miglitol In Rat Plasma Using Unique Solid‐Phase Extraction Coupled With Liquid Chromatography–Tandem Mass Spectrometry” Biomedical Chromatography, 28(10), 2014, 1423-1429.
72. M. V. Attimarad, A. B. Nair, & B. E. Aldhubaib, “Development Of Liquid Chromatographic Method For The Simultaneous Determination Of Metformin And Miglitol In Human Plasma: Application To Pharmacokinetic Studies,” Journal Of The Iranian Chemical Society, 12, 2015,1629-1636.
73. M. Rajput, M. Dahiya, P. Kumari, K. Kalra, M. Aggarwal, & R. K. Khandal, “Method Development And Validation For Determination Of Voglibose In Tablet Formulation Using Lc-Ms/Ms,” Journal Of Chemistry, 8, 2011, 1770-1783.
74. K. Ramakrishnab Et Al. “Development And Validation Of Lc Methods With Visible Detection Using Pre-Column Derivatization And Mass Detection For The Assay Of Voglibose,” 77(5), Mar 15 2009 1869-72. Doi :10.1016/J.Talanta.2008.09.041.
75. J. S. Woo, & J. K. Ryu, “Quantitative Determination Of Voglibose In Pharmaceutical Tablets Using High-Performance Liquid Chromatography–Fluorescence Detection With Post-Column Derivatization And Mass Spectrometric Detection,” Journal Of Pharmaceutical And Biomedical Analysis, 42(3), 2006, 328-333.