REVIEW ARTICLE

A Review of Various Analytical Techniques-Based Methods for Quantification of Sitagliptin (DPP-4 Inhibitor)

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Abstract

Sitagliptin is a commonly prescribed anti-diabetic drug that has been authorized for the treatment of Type 2 diabetes patients. Sitagliptin is a selective inhibitor of the dipeptidyl peptidase-4 enzyme. Accurate and exact measurement is essential for determining sitagliptin's pharmacokinetics, bioavailability, and therapeutic effectiveness. A variety of analytical methods have been developed for the measurement of Sitagliptin, over time, each with specific benefits and drawbacks. With the help of high-performance liquid chromatography, high-performance thin layer chromatography, liquid chromatography-mass spectrometry, spectroscopy (ultraviolet visible spectroscopy), electroanalytical methods, and ultraviolet performance liquid chromatography methods, this critical review aims to comprehensively evaluate the various analytical techniques used for sitagliptin quantification. The overview covers each technique's fundamental guiding concepts, sample preparation steps, and detection methods. Based on publicly available data, each method's performance qualities, including sensitivity, selectivity, accuracy, precision, and linearity, are evaluated rigorously. It is also explored whether these methods can be used on complicated biological matrices, including plasma, serum, and urine. The overview is concluded with a comparison of the various analytical approaches, highlighting their advantages and disadvantages. In addition, information on new developments and trends in sitagliptin measurement techniques is included.

Key words: Anti-diabetic, dipeptidyl peptidase-4 inhibitor, electroanalytical methods, high performance liquid chromatography, liquid chromatography with tandem mass spectrometry, ultraviolet

INTRODUCTION

Back in the year of 2009, it was sitagliptin that received market approval making itself the first in the category of dipeptidyl peptidase 4 (DPP-4) inhibitors in Japan. In other countries, it was launched in the USA in 2006, while in the UK market in 2007. The incretin effect, which is said to be the main device for the release of around 50% of the normal release of insulin, followed by glucose ingestion is significantly decreased in type 2 DM.[1] The biological importance of the class of DPP-4 has been studied in mice. It was observed that the mice were healthy, fertile, and have shown tremendous increase in their metabolic activities. In addition, to, they are resistant to diet-induced obesity and are insulin sensitive. The choice of sitagliptin in the class of DPP-4 is because of its competent and potent nature, followed by showing reversible inhibition of DPP-4 enzyme.[2] The structure of Sitagliptin is shown in Figure 1. It is said that sitagliptin is highly selective for DPP-4 but shows no effect on DPP-8 and 9 as these DPP-8 and 9 are very important, as their inhibition might cause serious toxicity.[3] Sitagliptin is very well tolerated, has moderate efficacy, and has weight weight-neutral oral antidiabetic agent. It has shown a particular effect in the management of diabetic patients having certain renal or hepatic dysfunctions. This class of drug is now approved in more than 130 countries and is extensively used as monotherapy and in combination with other antihyperglycemic drugs.[4]

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Received: 18-08-2025
Revised: 24-09-2025
Accepted: 30-09-2025

SYNTHESIS OF SITAGLIPTIN

Ye *et al.* produced sitagliptin by stereoselective enolate addition, followed by Pd-catalyzed decarboxylation to produce -amino-ester (2), which is then converted into tert-butyl sulfinyl aldimine (1), which was previously prepared by direct condensation of the commercially available aldehyde. After the chiral auxiliary is removed, the desired sitagliptin with good optical purity results from the saponification of the terminal ester and peptide-like coupling with the piperazine moiety (3). The synthesis of Sitagliptin is shown in Figure 2.[5,6]

MECHANISM OF ACTION

The basic action where sitagliptin shows its use is by complete inhibition of DPP-4 which is DPP-4 enzyme. The incretins Glucagon-like peptide-1 (GLP-1) and GLP, which become liberated after eating, may be broken down by this enzyme. They aid in the production of insulin and lessen the release of glucagon by the pancreatic beta cells by limiting the breakdown of GLP-1 and GLP. As a result, the blood glucose level returns to normal. The increase in insulin and drop in glucagon reduce when the blood level returns to normal, preventing hypoglycemia. In addition, to this, sitagliptin has shown lowering of hemoglobin A1C level by about 0.7% versus placebo.[7] The mechanism of action is shown in Figure 3.

ULTRAVIOLET-VISIBLE SPECTROSCOPY METHODS

It is possible to recover samples and separate pure substances effectively using ultraviolet visible spectroscopy (UV-VIS) without the need for derivatization, which is a straightforward and affordable method. Since the procedure doesn't cause any damage to the sample, it can be processed, used again, or subjected to more scrutiny. Measurements are easily included in experimental approaches since they can be quickly taken. Numerous sectors, including pharmaceuticals, environmental monitoring, food and beverage analysis, and chemical process control, frequently employ multicomponent UV analysis. It is an important technique in analytical chemistry and quality control because it helps researchers and analysts to swiftly and reliably ascertain the composition of complicated mixtures. However, the quality of the reference spectra and the appropriate selection of analytical techniques have a significant impact on the accuracy and dependability of the results. Many methods were developed for tablets and bulk formulation using solvent hydrochloric acid (HCL), water, and methanol at the wavelength of 267 nm absorption maxima using a double beam spectrophotometer[8-14] and one method developed in combination of solvents like HCl, sodium hydroxide (NaOH), H_2O_2 in the above same condition.[15] Moreover, one method for drug at the detection of wavelength 271 nm using water as solvent.[16] Amruta, Sujani and Bhavya shri *et al* developed methods for the combination of Sitagliptin and Metformin with water as a solvent at 266 nm and 232 nm for different formulations. Using a double-beam spectrophotometer, the same mixture and solvent were also discovered at various wavelengths.[17-19] The unique needs of the analysis, the accessibility of resources, and the required level of accuracy and precision must all be taken into account when choosing the optimal approach for a certain application. In addition, the choice of approach may also be influenced by variables like analysis time and cost. The provided methods are mentioned in Table 1.

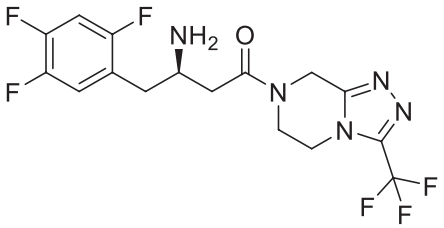

Figure 1: Structure of Sitagliptin

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

The HPLC is widely used as a separation technique for drugs along with the validated methods as per ICH guidelines. Few methods have been reported as sitagliptin being a single entity using C_{18} as column by taking different mobile ratios like KH_2PO_4, acetonitrile, DEA Acetonitrile, ammonium

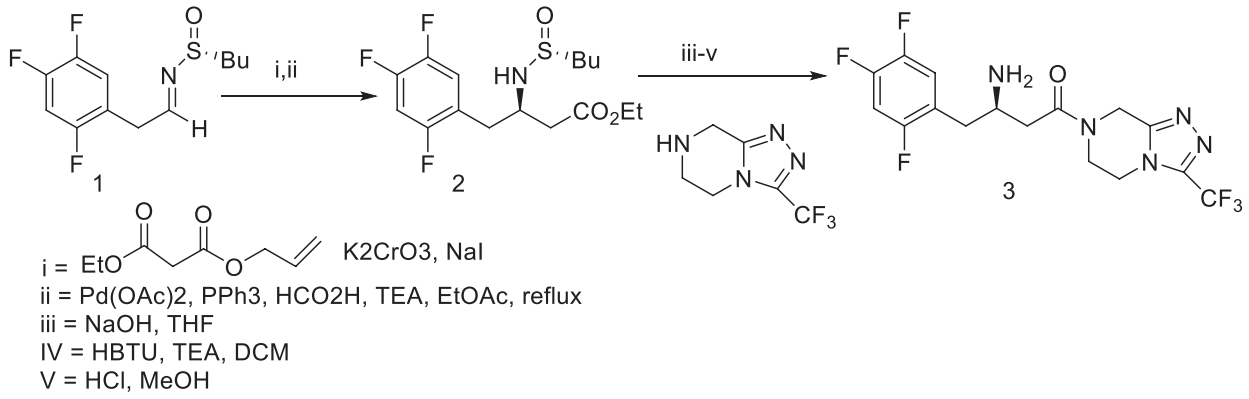

Figure 2: Synthesis of Sitagliptin

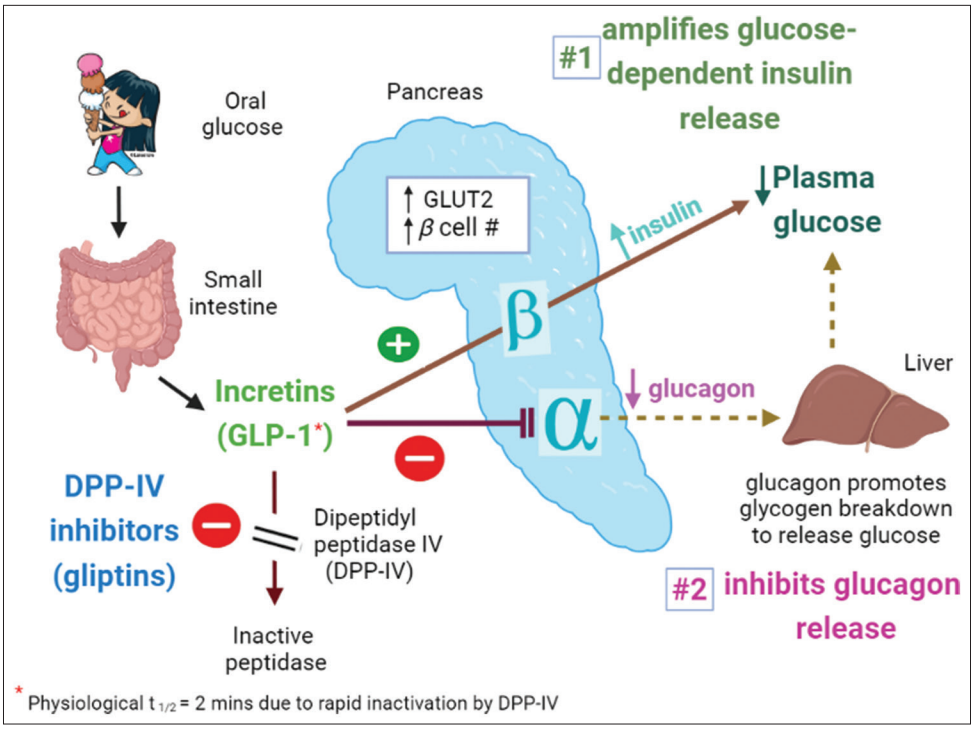

Figure 3: Mechanism of action of Sitagliptin

Table 1: Described spectrophotometric methods for Sitagliptin as an individual drug and with its combination

S. No.	Drugs	Matrix	Solvents	Spectrophotometer	Detection λ_{max} (nm)	Comments	References
1	Sitagliptin	Bulk	Methanol, Water	Double beam	267	Reproducible, Accurate, Precise, Reproducible, Sensitive	[12]
2	Sitagliptin	Tablet	HCl	Double beam	267	Simplicity, Economy, Rapid, Accurate, Precise	[8]
3	Sitagliptin	Bulk	HCl	Double beam	267	Precision Study, Accurate, Reproducible	[9]
4	Sitagliptin	Bulk, Tablet	HCl, NaOH, H_2O_2	Double beam	267	Simple, Economy, Rapid, Sensitive, Accurate	[15]
5	Sitagliptin	Tablet	Water	Double beam	271	Simple, Sensitive, Accurate, Precise	[16]
6	Sitagliptin	Tablet	Methanol, Water	Double beam	266	Simple, Accurate, Precise, Highly Sensitive, Reproducible, Inexpensive	[13]
7	Sitagliptin	Tablet	Water	Double beam	267	Economical, Simple, Precise, Accurate, Cost Effective	[11]
8	Sitagliptin	Bulk	HCl	Double beam	267	Simple, Precise, Accurate Method	[10]
9	Sitagliptin	Bulk, Tablet	Methanol, Water	Double beam	267	Accurate, Precise, Sensitive, Cost Effective, Minimal Maintenance	[14]
10	Sitagliptin Metformin	Bulk, Tablet	Water	Double beam	266 232	Accurate, Precise, Selective, Employed Successfully	[17]
11	Sitagliptin Metformin	Bulk, Tablet	Water	Double beam	267 232	Simple, Selective	[19]
12	Sitagliptin Metformin	Tablet	Water	Double beam	266 232	Simple, Rapid, Selective, Precise	[18]

HCl: Hydrochloric acid, NaOH: Sodium hydroxide

Table 2: Reported HPLC methods for Sitagliptin as a single entity and with its combined preparation

S. No.	Matrix	Drugs	Mobile phase (v/v)	Detection λ_{max} (nm)	Flow rate (mL/min)	Comments	References
1	Tablet	Sitagliptin	0.1 M KH_2PO_4:Acetonitrile (50:50)	268	1	Simple, Rapid, Sensitive, Accurate, Precise Rugged	[20]
2	Bulk	Sitagliptin	10 mM ammonium acetate: 0.5% DEA-Acetonitrile (40:60)	266	1	Simple, Rapid, Accurate, Precise, Robust, Selective, Sensitive	[21]
3	Bulk	Sitagliptin	(0.05 M) Phosphate Buffer: Acetonitrile (30:70)	255	1	Simple, Sensitive, Precision, Reproducibility	[22]
4	Bulk, Tablet	Sitagliptin	Methanol: Acetonitrile: 0.1% *ortho* phosphoric acid (40:55:05)	265	1	Rapid, Simple, Specific, Sensitive, Precise, Accurate, Reliable, effectively applied for Routine Analysis	[23]
5	Bulk	Sitagliptin	Perchloric acid: Methanol (70:30)	266	1	Linear, Accurate, Precise, Rapid, Specific	[24]
6	Bulk, Tablet	Sitagliptin	Methanol: Water: Triethylamine: Acetic acid (60:40:0.1:0.1)	268	0.5	Accuracy, Selectivity, Precision	[25]
7	Bulk	Sitagliptin	Methanol: Phosphate Buffer 10 mM PH-4.8 (60:40)	267	0.8	Simple, Precise, Accurate, Rapid	[26]
8	Bulk, Tablet	Sitagliptin	0.1 M KH_2PO_4:Methanol (50:50)	267	0.7	Simple, Accurate, Precise, Linear, Robust	[27]
9	Tablet	Sitgliptin	Phosphate Buffer (PH-6):Acetonitrile (70:30)	268	1	Time-saving, Rapid, Selective, Linear, Precise, Accurate, Robust	[28]
10	Tablet	Sitagliptin, Metformin	Acidified Water: Methanol (60:40)	260	1	Simple, Economic, ecologically technique, Linear, Precise, Accurate, Robust, Specific	[29]
11	Bulk	Sitagliptin, Metformin	MeOH, ACN, 0.01 mM KH_2PO_4 pH 3.5±0.5 (42.135:10:47.862)	210	0.484	Specific, Accurate, Linear, Precise, Robust	[30]
12	Tablet	Sitagliptin, Atorvastatin	10 mM Potassium dihydrogen: phosphate buffer (75:25)	218	1	Sensitive, Reliable, Accurate, Precise	[44]
13	Bulk Tablet	Sitagliptin, Metformin	10 mM KH_2PO_4 (pH: 3.00): Acetonitrile (65:35)	256	1	Simple, Economic, Rapid, Precise, Accurate, Specific	[36]
14	Tablet	Sitagliptin, Metformin	Acetonitrile: Phosphate Buffer (pH: 6.8) (40:60)	257	1	Simple, Precise, Accurate	[37]
15	Bulk	Sitagliptin, Ibuprofen	Methanol: Water (80:20)	275	1	Accurate, Precise	[45]
16	Tablet	Sitagliptin, Metformin	Methanol: Phosphate Buffer (KH_2PO_4) pH-3 (70:30)	258	1	Simple, Fast, Rapid, Accurate, Reproducible, Efficient	[38]
17	Bulk Tablet	Sitagliptin, Metformin	KH_2PO_4:Methanol (50:50)	215	1	Specific, Precise, Accurate, linear, Robust, Linear	[39]
18	Bulk Tablet	Sitagliptin, Metformin	Water: Methanol (60:40)	258	1	Simple, Precise Accurate, Rapid	[40]
19	Bulk Tablet	Sitagliptin, Ertugliflozin	0.1 M K_2HPO_4:Methanol (65:35)	225	1	Linearity, sensitivity, Accuracy, Precision, Selectivity, Robustness	[53]

(*Contd...*)

Table 2: (*Continued*)

S. No.	Matrix	Drugs	Mobile phase (v/v)	Detection λ_{max} (nm)	Flow rate (mL/min)	Comments	References
20	Bulk Tablet	Sitagliptin, Simvastatin	Acetonitrile: Buffer (80:20)	254	1	Simple, Reliable	[47]
21	Tablet	Sitagliptin, Metformin	Ammonium Acetate Buffer: MeOH (60:40)	265 225	1	Specificity, Linearity, Precision, Accuracy, Robustness	[41]
22	Tablet	Sitagliptin, Simvastatin	Phosphate Buffer: Acetonitrile (30:70)	254	1	Simple, Accurate, Cost-effective, Less time-consuming	[48]
23	Tablet	Sitagliptin, Metformin	0.1% H_3PO_4: Methanol (50:50)	260	1	Simple, Rapid, Precise, Accurate, Reproducible, Selective	[42]
24	Tablet	Sitagliptin, Metformin	Methanol: KH_2PO_4 Buffer (70:30)	266	1	Sensitive, Accurate, Reproducible	[43]
25	Tablet	Sitagliptin, Simvastatin	Methanol: Water (70:30)	253	1	Simple, Sensitive, Reproducible	[49]
26	Bulk Tablet	Sitagliptin, Ertugliflozin	KH_2PO_4 Buffer: Acetonitrile (70:30)	240	1	Simple, Accurate, Economical, Rapid	[54]
27	Bulk	Sitagliptin, Simvastatin	Methanol: Distilled Water (80:20)	254	1	New, Simple, Cost-Effective, Accurate, Safe, Free from Pollution, Precise	[50]
28	Tablet	Sitagliptin, Metformin	KH_2PO_4:Methanol (50:50)	260	1	Simple, Rapid, Precise, Reliable, Accurate, Economical	[31]
29	Bulk Tablet	Sitagliptin, Metformin	Acetonitrile: Phosphate Buffer 0.03 M (70:30)	218	1	Precise, Specific, Accurate, Stability indicating, Robust	[32]
30	Bulk Tablet	Sitagliptin, Metformin	Buffer: ACN (50:50)	285	1	Simple, Rapid, Accurate, Precise, Specific, Robust, Economical, Less time-consuming	[48]
31	Bulk Tablet	Sitagliptin, Metformin	Methanol: HPLC Grade Water (80:20)	254	0.8	Simple, Accurate, Precise	[33]
32	Tablet	Sitagliptin, Metformin	pH-9 Phosphate Buffer: Acetonitrile: Methanol (35:45:20)	260	0.6	Precise, Accurate, Selective, Robust, Reproducible, Rapid	[34]
33	Bulk Tablet	Sitagliptin, Metformin	OPA Buffer: Acetonitrile (80:20)	250	1	Simple, Precise, Accurate, Rapid	[35]

HPLC: High-performance liquid chromatography

acetate, phosphate, methanol, and perchloric acid along with triethylamine, acetic acid and water having buffers at a rate of 0.5–1 mL/min flowing between 255 and 268 nm using both tablet and bulk in different cases.[20-28] Other methods involved the combination of sitagliptin and metformin using C_{18} as column having different mobile phases like methanol, acidified water, acetonitrile, and others having buffer at 0.484–1 mL/min between 210 and 266 nm using both tablet and bulk have been identified by different researchers and are illustrated in the table given below.[29-43] Patel *et al*. used another technique where sitagliptin was combined with atorvastatin using 10 nM of potassium dihydrogen phosphate buffer flowing at 1 mL/min at 218 nm showed sensitivity, reliability, and accuracy.[44] Another method was developed by taking ibuprofen with sitagliptin at 275 nm having 1 mL/min flow using methanol and water at a ratio of 80:20 showed accuracy and precise nature which was developed by Rehman *et al*.[45] Sitagliptin when combined with ertugliflozin flowing at 1 mL/min at 225 nm and 240 nm using K_2HPO_4 with methanol and acetonitrile, respectively, showed linearity, sensitivity, robustness, and rapidness, which was developed by different researchers.[46] Apart from these, many researchers have also shown taking sitagliptin with simvastatin at 1 mL/min in different wavelengths using methanol, distilled water, water, acetonitrile, and phosphate buffer revealed results which have been tabulated in the table given below.[46-51] All developed methods for Sitagliptin as an individual drug and its combination are shown in Table 2.

Table 3: List of HPTLC methods for determination of Sitagliptin either alone or in the combined dosage form

S. No.	Drug	Matrix	Sorbent and mobile phase composition	Detection λ_{max} (nm)	Linearity (ng/spot)	Comments	References
1	Sitagliptin	Bulk	n- Butanol: Methanol: Water: Formic Acid (3:1:1: 0:1)	269	2000–7000	Simple, Inexpensive, Accurate, precise	[55]
2	Sitagliptin	Tablet	Toluene: Methanol (8:2)	265	2000–12000	Precise, Accurate, Reproducible, and stability-indicating	[56]
3	Sitagliptin, Metformin	Bulk Tablet	Acetone: Methanol: Toluene: Formic acid (4:3:2:1)	220	200–500 2000–5000	Advantage of sensitivity, Accuracy, Precision, Low cost	[58]
4	Sitagliptin, Metformin	Bulk	Methanol: Ammonia: Glacial acetic acid (9.4:0.4:0.2)	214	100–1100 1000–11000	Precise, Specific, Accurate Method	[59]
5	Sitagliptin, Metformin	Tablet	Butanol: Water: Glacial acetic Acid (6:2:2)	227	50–1000 500–10000	Simple, Precise, Sensitive, Accurate	[60]
6	Sitagliptin, Simvastatin	Tablet	Toluene: Methanol: Acetic Acid (5:4:1)	255	100–500 40–200	Accurate, Precise, Specific, Rapid Found to be suitable for quantitative analysis	[57]
7	Sitagliptin, Metformin	Bulk	Water: Methanol: Ammonium sulphate (4.5:4.5:1.5)	254	3000–24000 50–400	Precise, specific, accurate, stability-indicating, and robust	[32]

HPTLC: High-performance thin-layer chromatography

HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY

Apart from HPLC, an innovative method of high-performance thin-layer chromatography was studied, which has separate layers and has maximum efficiency. The literature survey showed that many papers have been developed using high-performance thin-layer chromatography (HPTLC) as a single entity as well as in combination with different drugs. Sitagliptin used in a bulk matrix having a linearity of 2000–7000 at 269 nm using n-butanol, methanol, water, and formic acid at a ratio using mobile phase composition was developed by Tumbare *et al.*[54] Similarly, for sitagliptin as a single entity in bulk form was developed at 267 nm at 1000–6000 linearity using methanol, water, and triethylamine by Jain *et al.*[55] Apart from sitagliptin being used individually, it when combined with simvastatin in a tablet matrix at 255 nm was developed by Ganesan and Thangarasu using toluene, methanol, and acetic acid at a ratio of 5:4:1.[56] Metformin, when combined with sitagliptin at different wavelengths, was developed by different researches and is mentioned in the table, which showed accuracy, precise nature, specificity, sensitivity, and low cost.[32,57-59] Various HPTLC methods for the determination of Sitagliptin either alone or in the combined dosage form are shown in Table 3.

CONCLUSION AND FUTURE PERSPECTIVE

The meticulous examination of the best optical methods, chromatographic analysis, and electro-analytical methods of sitagliptin in various preparations and conditions as an individual medicine and its combination. Furthermore, the most typical technique for evaluating the substance Sitagliptin is liquid chromatography. Sitagliptin quality may be measured and controlled using accurate, verified procedures. Thus, there is a large area of research in the field of HPTLC, LC-MS, HPLC, and UV methods of drug estimate. The future outlook for the analysis of sitagliptin and other pharmaceutical substances is positive as analytical technology continues to advance. The following are some crucial areas for improvement. The development of automated and miniaturized analytical equipment may result in the analysis of sitagliptin taking less time and using fewer samples. The drug analysis throughput is continually being increased by the pharmaceutical sector. Future analytical techniques should be created to meet this requirement, particularly for extensive quality control and bioavailability research. By reducing the production of hazardous waste and utilizing more environmentally friendly solvents and reagents, the use of green analytical chemistry concepts can aid in lowering the environmental effect of analytical operations. To ensure the consistency and comparability of results across various laboratories and research investigations, further efforts should be made to standardize analytical procedures for sitagliptin. The sensitivity and specificity of sitagliptin quantification can be improved, especially in complex matrices, by advances in mass spectrometry such as tandem mass spectrometry (MS/MS) and high-resolution mass spectrometry. Determining the shelf life and degradation products of sitagliptin in pharmaceutical formulations will need the development of stability-indicating technologies. The combination of several

analytical methods (such as HPLC-MS and UHPLC-MS/MS) can yield complementary data and boost confidence in the outcomes. To better understand the pharmacokinetic behavior of sitagliptin and optimize dosing regimens, future analytical investigations can concentrate on combining pharmacokinetic modeling with analytical data. The adoption of cutting-edge analytical techniques like microfluidics, nanotechnology, and biosensors may create new opportunities for sitagliptin research. In conclusion, the analysis of analytical techniques for sitagliptin has brought to light the present advantages and disadvantages of existing methodologies. The accuracy, effectiveness, and usefulness of sitagliptin analysis may be further improved in many research and pharmaceutical applications by embracing technology improvements and taking into account future views.

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Source of Support: Nil. **Conflicts of Interest:** None declared.