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Review article

Sitagliptin in diabetes management: a comprehensive review of therapeutic advantages, formulation challenges, and analytical strategies for oral solution development

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ABSTRACT

Sitagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor that has emerged as a mainstay in the treatment of type 2 diabetes mellitus (T2DM) on account of favourable efficacy, safety and tolerability profile. In this comprehensive review, we discuss the therapeutic advantages of sitagliptin, including its glucose-dependent mechanism of action, low risk of hypoglycemia, weight neutrality and proven cardiovascular safety as demonstrated by the landmark TECOS trial. The tablet formulation has been successful in clinical trials but there are large patient populations (paediatric, geriatric, dysphagic and critically ill) that require alternative liquid dosage forms. The formulation challenges of developing a stable sitagliptin oral solution are discussed, in relation to the moisture sensitivity of the drug, pH-dependent stability and the need to optimise palatability. A critical review of recent patent disclosures and formulation studies in the scientific literature shows that judicious selection of buffering agents (pH 4–6), artificial sweeteners (sucralose, acesulfame-K), preservatives (parabens) and thickening agents (hydroxyethylcellulose) are required for the successful development of an oral solution. Moreover, the review summarises the current literature on the development of analytical methods, emphasising the role of reverse-phase high-performance liquid chromatography (RP-HPLC) and the increasing application of Analytical Quality by Design (AQbD) principles for the development of stable and robust assay methods. Formulation science, analytical chemistry and patient-centric design principles can together meet the unmet clinical need for a commercially available, stable and quality-controlled oral solution of sitagliptin.

Keywords: Sitagliptin, DPP-4 inhibitors, Formulation development, RP-HPLC, Analytical quality by Design.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most important issues of public health in the 21st century. The International Diabetes Federation estimated that about 537 million adults aged 20-79 years had diabetes in 2021, and this is projected to increase to 783 million by 2045. India alone has over 77 million people with diabetes, the second-largest number in the world. The economic toll is just as staggering, with global healthcare costs for diabetes management alone exceeding USD 966 billion [1].

Regrettably, although 91.4% of those diagnosed are treated, only 41.6% are optimally controlled in terms of glycemia. Despite the wide availability of therapeutic options, this gap in therapy persists, indicating that diabetes management remains suboptimal in most settings. The pathophysiology of T2DM is characterised by a dual defect, consisting of peripheral insulin resistance in muscle, liver and adipose tissue, and progressive dysfunction and loss of pancreatic β-cells. Uncontrolled hyperglycemia results in microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular events (myocardial infarction, stroke, peripheral arterial disease). Thus, the goal of diabetes management remains to achieve and maintain glycaemic control, which is typically defined as glycosylated haemoglobin (HbA1c) values of less than 7% [2].

The evolving therapeutic landscape

The current-day paradigm shift in diabetes management. Current guidelines from the American Diabetes Association and European Association for the Study of Diabetes recommend a personalised, multifactorial approach that includes lifestyle modification and individualised pharmacotherapy.

The traditional "treat-to-target" approach, which has focused on glycaemic control alone, has been supplemented with a "treat-to-benefit" approach emphasising cardiovascular and renal protection, weight effects and safety. The best management requires the combination of both procedures, to be followed in parallel and in a coordinated manner.

DPP-4is play a particular role in this therapeutic setting. They provide clinically meaningful reduction in HbA1c, with almost no risk of hypoglycaemia, neutral effect on weight, favourable cardiovascular safety profile and limited adverse effects. These properties make DPP-4is ideal candidates for combination therapy, intending to achieve both glycaemic targets and broader metabolic and organ protective benefits. Sitagliptin, the first DPP-4 inhibitor approved by the U.S. FDA, has accumulated significant clinical experience and remains a flexible option for bridging the "treat-to-target" and "treat-to-benefit" paradigms [3].

Therapeutic advantages of sitagliptin

Mechanism of action

Sitagliptin is a competitive inhibitor of dipeptidyl peptidase-4 (DPP-4) enzyme. This enzyme is responsible for the degradation of incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) released from the gut in response to food intake. Sitagliptin inhibits DPP-4, prolonging the half-life of active GLP-1 and GIP, resulting in:

Elevated glucose-stimulated insulin secretion from pancreatic β-cells

Suppression of glucagon secretion from pancreatic α-cells

Delayed gastric emptying

Improved β-cell survival

Importantly, this mechanism is glucose-dependent: as blood glucose levels normalise, GLP-1 concentrations decrease, and the pharmacological effect of sitagliptin diminishes. This is a built-in safety feature that abolishes the dangerous hypoglycemic episodes seen with sulfonylureas or insulin therapy.

Glycemic efficacy

Clinically important reductions in HbA1c, usually in the 0.65% to 1.0% range, are observed after 12 to 52 weeks of therapy with sitagliptin. The drug has demonstrated consistent efficacy as monotherapy, initial combination therapy with metformin or as add-on therapy to sulfonylureas or insulin. Standard doses are 25 mg, 50 mg or 100 mg once daily depending on renal function. It has a longer half-life of about 12 to 14 hours, which means that a single dose can maintain DPP-4 inhibition over the full 24-hour period, enabling once-daily oral dosing.

Safety profile and cardiovascular outcomes

DPP-4 inhibitors are well tolerated and have similar rates of adverse effects compared with placebo. Sitagliptin has been well studied in the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial, which enrolled more than 14,000 patients with established cardiovascular disease. The trial definitively showed that sitagliptin did not increase the risk of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. The hazard ratio for MACE was 0.98 (95% CI: 0.88–1.09), confirming non-inferiority to placebo. Additionally, sitagliptin was not linked to an increased risk of hospitalisation for heart failure (HR: 1.00, 95% CI: 0.83–1.20).

Emerging data suggest cardiovascular benefits of sitagliptin beyond its glucose-lowering effects. Preclinical and clinical studies have shown potential anti-inflammatory, antioxidant and anti-apoptotic effects. Sitagliptin has been shown to inhibit monocyte migration, decrease proinflammatory cytokines, modulate platelet function, and promote reverse cholesterol transport. Sitagliptin improved cardiac function in models of heart failure in a preclinical study, possibly by modulating inflammation and oxidative stress.

Renal safety and dose adjustability

Sitagliptin is predominantly eliminated in the urine as unchanged drug (approximately 79% of an oral dose). This pharmacokinetic property necessitates dose adjustment in renal impairment:

Mild impairment: 100 mg per day

Moderate impairment: 50 mg once daily

Severe impairment or end-stage renal disease: 25 mg once daily

This flexibility permits prescribers to continue DPP-4 inhibitor therapy across a wide range of chronic kidney disease without accumulation of toxic metabolites. Moreover, sitagliptin lacks nephrotoxicity and has not been associated with acute kidney injury when used in appropriate use [4, 5].

Drug-excipient compatibility considerations

The compatibility of sitagliptin with the pharmaceutical excipients is an important factor in formulation development. The interaction of sitagliptin with various pharmaceutical excipients commonly used was studied by differential scanning calorimetry (DSC) compatibility study. The study showed a sharp endothermic peak of sitagliptin at 212.1 °C with ΔH of 131.5 J/g, which was attributed to the melting of the drug. In some of the mixtures, the disappearance of the sharp melting endothermic peak was observed in some combinations indicating the facile transformation of dehydrated sitagliptin to its monohydrate form.

DSC results showed that sitagliptin was compatible with microcrystalline cellulose, croscarmellose and pregelatinized starch. However, some excipient interactions were observed with magnesium stearate, ascorbic acid and citric acid. X-ray diffractometry and FT-IR were used as supportive tools to interpret the DSC results. Such compatibility findings are of basic importance for the rational selection of excipients in the development of solid and liquid dosage forms [6].

Summary of therapeutic advantages

Sitagliptin offers a compelling combination of therapeutic advantages:

Minimal risk of hypoglycemia

Weight neutrality

Proven cardiovascular safety (TECOS trial)

Renal dose adjustability

Low drug-drug interaction potential (minimal CYP metabolism)

Once-daily oral dosing

Excellent synergy with other antidiabetic agents

Favourable gastrointestinal tolerability

Potential pleiotropic (anti-inflammatory, cardioprotective) benefits

Formulation challenges for oral solution development

The rationale for oral liquid formulations

Sitagliptin has been clinically successful as a tablet formulation, but there are still considerable patient populations who have difficulty swallowing solid dosage forms. These include

Paediatric population: More and more are diagnosed with type 2 diabetes as childhood obesity rises

Geriatric patients: Often have dysphagia due to stroke, Parkinson's disease, dementia or polypharmacy

Critically ill or unconscious patients: Need to be given enterally via nasogastric tubes

Bariatric surgery patients: Altered GI anatomy

Patients with head and neck cancers or strictures of the oesophagus

Oral solutions have important advantages in these populations: rapid absorption, improved bioavailability, ease of administration, dose flexibility (10–25 mg increments) and better patient compliance. A commercially available oral solution would allow prescribers to titrate the dose based on blood glucose monitoring, a capability not available with fixed-dose tablets.

Moisture sensitivity

Sitagliptin is a moisture-sensitive active pharmaceutical ingredient (API) and is well known. Direct compression is difficult because of poor flowability and low compatibility of the drug during tablet manufacturing. The moisture sensitivity of the oral solutions translates into chemical instability in aqueous environments. Sitagliptin is most stable at pH 4-6 and degrades under strongly acidic and alkaline conditions. This calls for careful control of pH and the use of suitable buffering agents to maintain stability throughout the shelf-life of the product [7].

Formulation composition requirements

Patent disclosures and formulation studies have established key requirements for a stable sitagliptin oral solution. The aqueous liquid oral gliptin composition typically comprises:

Table 1: Formulation composition and functional roles of ingredients

Component	Concentration	Function
Sitagliptin (or salt)	2.5–3.5% w/v	Active ingredient
Artificial sweetener	1–5% w/v	Taste masking
Thickening agent	0.1–2.0% w/v	Viscosity enhancement
Buffering agent	0.1–1.0% w/v	pH control
Preservative	0.1–0.5% w/v	Antimicrobial
Antioxidant	0.01–0.10% w/v	Stability enhancement
Chelating agent	0.01–0.1% w/v	Metal ion sequestration
Flavoring agent	As required	Palatability

Key formulation variables

pH and buffering

Oral solution: The pH of the solution is essential for sitagliptin stability. Patent disclosures suggest a pH range of 3 to 8 is acceptable; a more targeted range is 4 to 7, and optimal stability is at a pH of 5.5 to 5.8. Buffers based on citrate (e.g. trisodium citrate dihydrate) are often used to keep the pH in this range. Selection of suitable buffering agents is very important to prevent pH drift during storage which can affect drug stability.

Sweetening agents

Sitagliptin is bitter, and this needs to be masked to achieve patient acceptability.

Artificial non-sugar alcohol sweeteners are better, especially blends such as:

Sucralose (0.8-2.0% w/v)

Acesulfame-K (0.2-1.0 % w/v)

Saccharin sodium

Thus, these agents do not contribute any sugar content and are suitable for diabetic patients. The composition should preferably have a sugar alcohol content of less than 10-25% w/v in an effort to reduce the risk of osmotic diarrhoea, especially in the pediatric population. The sugar alcohol content should be less than 25 w/v%, preferably less than 20 w/v%, most preferably less than 5 w/v% or without sugar alcohols (see patent literature).

Thickening agents

Thickening agents improve organoleptic properties and stability of oral solutions due to their ability to increase viscosity and prevent sedimentation. Suitable agents are: hydroxyethyl cellulose, hydroxypropyl cellulose, sodium alginate, sodium carboxymethylcellulose, gellan gum. Typical concentrations are 0.1-2.0% w/v, preferably 0.4-0.6% w/v. The patent literature suggests that thickening agents may improve the organoleptic experience and the stability of the solution.

Preservatives and antioxidants

Preservatives like methyl paraben, ethyl paraben, propyl paraben or butyl paraben are used to check the growth of microorganisms. To prevent oxidative degradation, antioxidants (eg, butylated hydroxyanisole) and chelating agents (eg, disodium edetate) are added. To improve long-term stability, an antioxidant should be added at concentrations of 0.01–0.10 w/v% [8].

Flavoring agents

Flavouring agents are needed to make the product palatable, especially for paediatric patients. Suitable flavours include forest fruits, strawberry, raspberry, cherry, cranberry, blueberry, blackcurrant, redcurrant, gooseberry and lingonberries. Selection and concentration of flavour should be optimised to mask the sitagliptin bitter taste without irritation.

Stability considerations

The patent disclosures and independent stability studies both indicate that properly formulated oral solutions of sitagliptin can be very stable. A stability study of sitagliptin phosphate (SiP) oral solution indicated that the formulations had drug concentrations near to 100% after 4 weeks of storage at room temperature (25°C, 60% RH) and accelerated stability conditions (40°C, 75% RH). The pH of the solution was constant during the study period, and the total impurities were less than 0.08%.

Relevant literature findings on stability

Less than 1% total impurities after 9 months at 25°C/60% RH

Total impurities < 1.5 % after 24 months at 25°C/60% RH

Remaining drug after 18 months at 25°C/60% RH is at least 95%

Microbial limits in acceptable pharmacopeial standards

The PLOS ONE study reported the development of an oral solution of sitagliptin (10 mg/ml) and its stability study at room temperature and under accelerated conditions (40°C/75% RH). The formulation was found to be stable for a period of 28 days, with organoleptic properties, pH, assay and related substances within acceptable limits. This confirms the possibility of developing a stable oral liquid formulation.

Extemporaneous formulation studies

The feasibility of preparing sitagliptin oral solutions extemporaneously for patients with swallowing difficulties has been evaluated in several studies. A study by Abu Salah et al. prepared different sitagliptin solution formulations using pure sitagliptin phosphate powder as the source of API. The formula rated highest for clarity and acceptable taste was selected for stability studies. The produced solution maintained its pH and did not show any microbial contamination, indicating good stability for a period of four weeks under two conditions (24°C/40% humidity and 40°C/70% humidity). This study provides a practical solution for patients with swallowing difficulties or feeding tubes who are not able to take oral solid dosage forms. Community chemists can prepare the solution using sitagliptin powder.

Analytical strategies for sitagliptin evaluation

Importance of analytical method development

All pharmaceutical products need to be subjected to stringent analytical testing to ensure their quality, safety and efficacy. Analytical methods for sitagliptin oral solutions should be able to accurately quantify the drug in the presence of excipients, preservatives, flavouring agents and possible degradation products. Without reliable analytical methods, even the best formulated oral solution cannot be guaranteed to contain the labelled dose, remain stable over its shelf life, or be free of toxic degradation products.

RP-HPLC as the method of choice

Reverse Phase High-Performance Liquid Chromatography (RP-HPLC) is the most reliable analytical technique for quantitative estimation of sitagliptin due to its high sensitivity, specificity, accuracy and reproducibility. In RP-HPLC, a non-polar stationary phase (C18 or C8 bonded silica) and a polar mobile phase (water mixed with organic solvents such as acetonitrile or methanol) are used. The method separates drug molecules from excipients, preservatives and degradation products on the basis of their hydrophobicity. RP-HPLC has several advantages for sitagliptin, such as:

Detection limits as low as 0.1 µg/mL

Linearity over a wide concentration range

Ability to resolve the drug from potential degradants

Compatibility with aqueous formulations

Analytical method development approaches

Traditional method development

Traditional analytical method development for sitagliptin has employed various techniques. A review of the literature reveals typical RP-HPLC conditions for sitagliptin analysis:

Parameter typical range

Column C18 or C8 (150–250 mm × 4.6 mm, 5 µm)

Mobile phase Phosphate buffer: acetonitrile/methanol (20:80 to 70:30)

pH 3.0–5.4

Flow rate 0.8–1.0 mL/min

Detection wavelength 210–282 nm

Retention time 2.0–6.5 minutes

Ali et al. have developed a rapid and sensitive RP-HPLC method for simultaneous determination of sitagliptin and metformin HCl using a Luna Phenomenex C8 column (4.6 × 250 mm, 5 µm) at room temperature. The mobile phase was 0.1% ortho-phosphoric acid, potassium dihydrogen phosphate buffer (pH 3.0) and acetonitrile in the ratio of 35:35:30. Symmetrical peaks were obtained for both drugs. Detection was performed at 210 nm with a flow rate of 1.0 mL/min. The method was linear in the concentration range of

2.5-7.5 ppm for sitagliptin and 25-75 ppm for metformin HCl. Assay recoveries were 100.36% and 100.20%, respectively, and LOD and LOQ for sitagliptin were found to be 0.201 ppm and 0.301 ppm.

Jayavarapu et al, developed a method using an Agilent C8 column with phosphate buffer (pH 6.26): acetonitrile in the ratio of 25:75 at a flow rate of 0.8 mL/min. The retention time of sitagliptin was found to be 6.528 min, and that of simvastatin was 2.475 min. The method was validated for system suitability, specificity, linearity, accuracy, precision, ruggedness and robustness as per ICH guidelines and used for stability studies (short, long and auto-sampler) and forced degradation studies (acidic, alkaline, oxidative and photolytic).

Analytical quality by design (AQbD)

The Analytical Quality by Design (AQbD) has been developed from the Quality by Design (QbD) philosophy to analytical method development. This systematic approach consists of:

Development of the Analytical Target Profile (ATP)

Risk analysis for defining Critical Method Variables (CMVs)

Use of Design of Experiments (DoE) for optimisation of method parameters

Define the Method Operable Design Region (MODR)

Model validation within the design space

AQbD has recently been successfully applied in the development of analytical methods for sitagliptin. Gurrala et al have developed and validated a stability-indicating RP-HPLC method for the analysis of sitagliptin and ertugliflozin in a fixed-dose combination using AQbD concepts. After a Box-Behnken design with response surface analysis, the Pareto risk assessment and Plackett-Burman screening design were used to define critical method variables. Multiple response optimisation (Derringer's desirability) was employed to optimise the critical method parameters such as % acetonitrile (X1), buffer pH (X2), and column oven temperature (X3). The analytes were separated with good resolution on a PRONTOSIL C18 column at 37 degrees C with a mobile phase of acetonitrile: acetate buffer, pH 4.4 (36:64% v/v) at a flow rate of 1 mL/min and detection at 225 nm. Linearity was found in the range of 25-150 µg/mL and 3.75-22.5 µg/mL for sitagliptin and ertugliflozin, respectively, at the retention times of 2.82 and 3.92 min, respectively. The method satisfied all the validation parameters of ICH Q2(R1) guidelines.

The AQbD approach has significant benefits

Better understanding of method capabilities and limitations

Increased chance of successful downstream method validation and transfer

Creation of a design space for method operating conditions

Inherent robustness to variations in method parameters

Regulatory flexibility within the approved method operable design region

Method validation parameters

The developed analytical method should be validated as per ICH Q2(R1) or Q2(R2) guidelines to prove the suitability for the intended purpose. Key parameters used for validation are:

Particularities

Ability to separate the analyte from degradation products, impurities and excipients. For stability-indicating methods, specificity should be demonstrated by means of forced degradation studies (hydrolytic, oxidative, photolytic and thermal stress). The purity of the sitagliptin peak in all the stress samples should be validated by the peak purity data from PDA detection. Studies on saxagliptin (a related DPP-4 inhibitor) have shown significant degradation under acidic and alkaline conditions while remaining stable under other stress conditions, indicating the importance of the forced degradation studies [9].

Linearity and range

Exhibits a proportional relationship between concentration and detector response over the desired range. Calibration curves were prepared with correlation coefficients (r2) of 0.999 or greater. Linearity has been confirmed for sitagliptin within ranges of 2.5–7.5 ppm, 10–90 µg/mL and 25–150 µg/mL as a function of the method and application.

Correctness

Evaluated by recovery studies by spiking known amounts of the drug into placebo. Recoveries are generally acceptable between 98 and 102%, and recoveries of 100.36% for sitagliptin have been published in studies.

Accuracy

Repeatability (intra-day precision) and intermediate precision (inter-day precision) are included. Acceptable precision is considered when relative standard deviation (RSD) values are < 2%. The robustness and ruggedness studies are usually conducted over the range of 0.28 to 0.57 RSD values.

Robustness

The robustness of the method to small, deliberate variations in method parameters such as flow rate, mobile phase composition, pH and column temperature.

Limit of detection (LOD) and limit of quantification (LOQ)

LOD is the lowest amount of analyte that can be detected (signal-to-noise ratio is normally 3:1), and LOQ is the lowest amount that can be reliably quantified (signal-to-noise ratio is normally 10:1). LOD and LOQ for sitagliptin have been reported as low as 0.201 ppm and 0.301 ppm, respectively, showing excellent sensitivity [10, 11].

Stability-indicating method

A stability-indicating analytical method is important to ensure the quality of the product up to its shelf life. These methods should be capable of accurately quantifying sitagliptin in the presence

of its degradation products, which may be generated during forced degradation studies. Important considerations are:

Forced Degradation Studies: Carried out under acid hydrolysis, alkaline hydrolysis, oxidative stress, photolytic stress, thermal stress and hydrolytic stress conditions

Mass Balance: minimum 95% recovery of drug under all stress conditions

Structural characterisation of degradation products by LC-MS, NMR and IR spectroscopy

Recent developments in analytical method development

Recent trends in analytical method development of sitagliptin have been focused on simultaneous determination in combination products. Given the growing trend of fixed-dose combinations for diabetes management, methods that can evaluate sitagliptin with other antidiabetic agents are of great interest:

Sitagliptin and Metformin: Developed C8 column-based methods with phosphate buffer (pH 3.0) and acetonitrile having excellent linearity and recovery

Sitagliptin and Simvastatin: Simultaneous estimation of Sitagliptin and Simvastatin by C8 column methods with phosphate buffer (pH 6.26) and acetonitrile has been validated.

Sitagliptin and Ertugliflozin: The AQbD-based approaches with C18 columns using acetate buffer have been reported

Integration of formulation and analytical strategies

A consolidated QbD framework

The integration of formulation and analytical method development in a Quality by Design framework offers an in-depth approach for sitagliptin oral solution development. Key components are:

Quality Target Product Profile (QTPP): Defining the desired quality attributes

Critical Quality Attributes (CQAs): Identification of attributes like assay, content uniformity, dissolution and stability

Risk Assessment: Application of Ishikawa diagrams and FMEA for critical variables identification

Design of Experiments for optimisation of formulation and method parameters.

Design Space: Defining combinations of variables in multiple dimensions to assure quality

Control strategy

Controls to be applied to raw materials, manufacturing and in-process monitoring.

Formulation for the patient

The development of sitagliptin oral solution is a patient-centric approach to diabetes management. Key patient considerations are as follows:

Taste appeal: Good taste masking by using suitable sweeteners and flavours

Dose Flexibility: Titration with Blood Glucose Monitoring

Administration: Suitable for patients with dysphagia or who need enteral administration

Stability: Preservation of product quality over shelf life

Compliance: Minimising pill burden and enhancing adherence

Regulatory aspects

The preparation of sitagliptin oral solution must meet the regulatory requirements:

ICH Guidelines: Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality System), Q2(R1) (Validation of Analytical Procedures)

USP, EP, IP monographs of sitagliptin Pharmacopeial Standards

Stability Testing: ICH Q1A(R2) for stability testing

Container Closure Systems: Proper packaging for product integrity

Future perspectives and research directions

Few technologies in drug delivery

Recently, new approaches to deliver the drug sitagliptin have been studied. Sitagliptin oral delivery has been tested with pectin-chitosan composite sustained-release formulations based on montmorillonite clay. The mechanical strength, swelling capability, and UV transparency of these composites were determined, and FTIR, SEM, XRD and DSC were used for their characterisation, and their physical and chemical properties were evaluated. In vitro studies under physiological conditions showed that 38% of the drug was released in the acidic medium of the stomach and a sustained release pattern was observed for the small intestine. The drug release kinetics demonstrated the highest correlation with the Korsmeyer-Peppas model, suggesting that diffusion was the main mechanism responsible for drug release from a polymeric matrix [12].

Exploring new excipients

The compatibility studies that show the interactions between sitagliptin and some excipients (such as magnesium stearate, ascorbic acid and citric acid) underline the requirement of extensive preformulation screening for the novel formulation development. Future studies should focus on the following:

Identification of other excipients compatible with sitagliptin

Developing formulations that ensure drug stability over extended shelf life

Optimisation of sweetener and flavour combination for paediatric acceptability

Development of sophisticated analytical methods

The application of AQbD principles in analytical method development is increasing. Future research directions are:

Development of AQbD-based methods for sitagliptin in various dosage forms

Methods for simultaneous determination in more complex combinations

Application of green chemistry principles for the reduction of solvent use and environmental impact [13].

CONCLUSION

Sitagliptin is an attractive option for the management of type 2 diabetes with a compelling combination of therapeutic advantages including minimal risk of hypoglycemia, weight neutrality, proven cardiovascular safety, renal dose adjustability and low potential for drug-drug interactions. Despite the clinical success of this drug in a tablet formulation, large patient populations including paediatric, geriatric, dysphagic and critically ill patients require alternative liquid dosage forms.

To develop a stable oral solution of sitagliptin, careful design of the formulation is needed to address the moisture sensitivity of the drug and its pH-dependent stability. Recent patent disclosures and formulation studies indicate that a successful oral solution formulation requires:

pH control from 4 to 6 with citrate buffers

Taste masking with artificial sweeteners (sucralose, acesulfame-K)

Parabens for antimicrobial preservation

Cellulose-based thickeners for increasing viscosity

Addition of antioxidant and chelating agent for stability.

Analytical method development is also critical for ensuring product quality. The method of choice for quantification of sitagliptin is RP-HPLC due to its high specificity, sensitivity and reproducibility. By applying Analytical Quality by Design (AQbD) principles such as risk assessment, Design of Experiments and determination of the Method Operable Design Region, a systematic approach can be adopted for the development of robust stability-indicating methods validated according to ICH guidelines.

The integration of formulation science, analytical chemistry and patient-centric design principles within a QbD framework offers a holistic approach to addressing the unmet clinical need for a commercially available, stable and quality-controlled sitagliptin oral solution. The successful development would greatly improve diabetes care in vulnerable patient populations and serve as a template for the development of oral liquid formulations of other BCS Class III/IV drugs.

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