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Polymorphic Transformations and in Vitro Bioequivalence Assessment of Saxagliptin Hydrochloride Solid Forms

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KEYWORDS

Saxagliptin hydrochloride, Polymorphism, Polymorphic transformation, In vitro bioequivalence, Solid-state characterization, Dissolution study, PXRD, DSC

ABSTRACT:

Saxagliptin hydrochloride, a dipeptidyl peptidase-4 (DPP-4) inhibitor widely used in the treatment of type 2 diabetes mellitus, can exist in multiple polymorphic forms that may significantly influence its physicochemical and biopharmaceutical properties. Polymorphism plays an important role in determining drug solubility, dissolution rate, stability, and ultimately its bioavailability. Therefore, understanding the polymorphic behavior of saxagliptin hydrochloride is essential to ensure consistent drug performance and therapeutic effectiveness. The present study investigates the polymorphic transformations of saxagliptin hydrochloride and evaluates their impact on in vitro bioequivalence. Different solid forms of saxagliptin hydrochloride were prepared and subjected to polymorphic transformation studies under controlled environmental and processing conditions. The obtained polymorphs were characterized using analytical techniques including powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). These characterization methods were employed to identify variations in crystalline structure, thermal properties, and molecular interactions among the different solid forms. Furthermore, in vitro dissolution studies were conducted under simulated gastrointestinal conditions to evaluate the pharmaceutical performance of each polymorphic form. Dissolution profiles were analyzed and compared using model-independent approaches to determine similarity and assess their bioequivalence potential. The results indicate that variations in crystal structure can influence the dissolution behavior of saxagliptin hydrochloride, which may subsequently affect its absorption characteristics. Overall, the findings emphasize the significance of polymorphic control during pharmaceutical development and manufacturing processes. A detailed understanding of polymorphic transformations assists in selecting the most stable and pharmaceutically suitable solid form, ensuring consistent dissolution performance and reliable therapeutic outcomes. In addition, in vitro bioequivalence studies provide an effective approach for evaluating the impact of polymorphism on drug formulation and quality control.

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Introduction

Polymorphism is a common phenomenon in pharmaceutical solids where a single chemical compound can exist in more than one crystalline form. These polymorphic forms possess identical chemical composition but differ in molecular arrangement and crystal packing, which can lead to variations in their physical and chemical properties. Such differences may significantly influence important pharmaceutical parameters including solubility, dissolution rate, stability, compressibility, and bioavailability. Consequently, polymorphism has become a critical consideration during drug development, formulation, and quality control to ensure the safety and therapeutic effectiveness of pharmaceutical products. Saxagliptin hydrochloride is an orally administered antidiabetic drug belonging to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors. It is widely prescribed for the management of type 2 diabetes mellitus by enhancing incretin hormone activity, which improves insulin secretion and reduces glucagon release in a glucose-dependent manner. Due to its therapeutic importance and widespread clinical use, maintaining consistent physicochemical and biopharmaceutical characteristics of saxagliptin hydrochloride is essential.

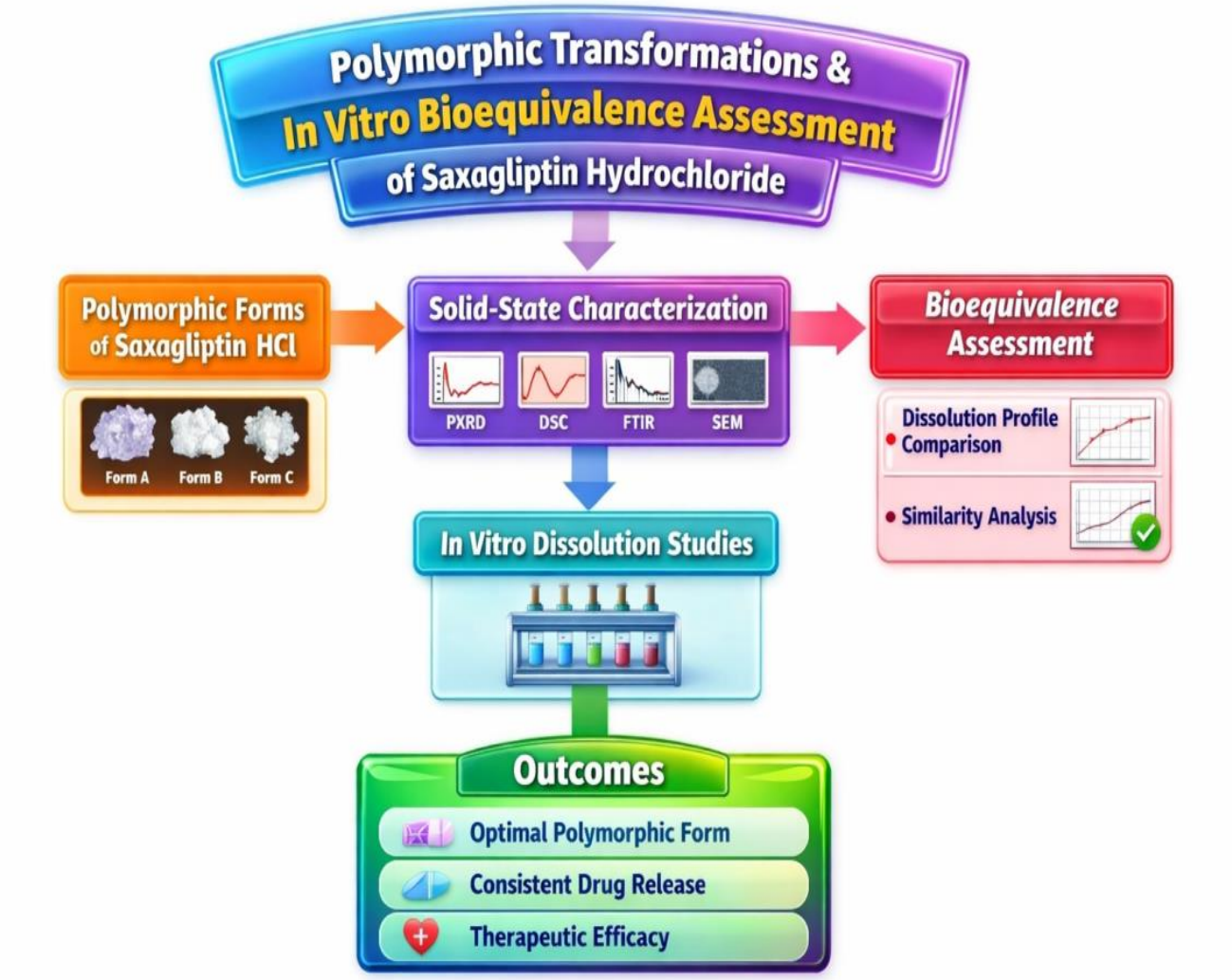

Chart 1 : Flowchart of Polymorphic Transformation and In Vitro Bioequivalence Assessment of Saxagliptin Hydrochloride

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The presence of multiple polymorphic forms may lead to differences in dissolution behavior and drug absorption, ultimately affecting bioavailability and therapeutic efficacy. For this reason, detailed investigation of polymorphic transformations is necessary to identify stable and pharmaceutically acceptable solid forms suitable for formulation. Solid-state characterization techniques such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM) are widely employed to analyze structural and thermal variations among polymorphs. In addition to solid-state characterization, in vitro bioequivalence studies play an important role in evaluating the pharmaceutical performance of different polymorphic forms. Dissolution testing under simulated physiological conditions provides valuable information regarding drug release behavior and helps predict in vivo drug absorption. Comparative analysis of dissolution profiles enables the assessment of similarity between formulations and ensures consistent product quality. Therefore, the present study focuses on investigating polymorphic transformations of saxagliptin hydrochloride and assessing their potential impact on in vitro bioequivalence. Understanding these aspects is essential for selecting the most suitable solid form during drug development and ensuring reliable therapeutic performance.

Review of Literature

Polymorphism is a widely recognized phenomenon in pharmaceutical sciences in which a single chemical substance exists in multiple crystalline forms. Although the chemical composition of these forms remains identical, differences in molecular arrangement within the crystal lattice can lead to significant variations in physicochemical properties such as melting point, solubility, dissolution rate, density, and stability. These variations can ultimately influence the drug's bioavailability and therapeutic performance. For this reason, polymorphic characterization has become a critical component of pharmaceutical research, drug development, and regulatory evaluation. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) emphasize the importance of identifying and controlling polymorphic forms during the development and manufacturing of active pharmaceutical ingredients (APIs). In recent decades, several pharmaceutical compounds have demonstrated significant changes in drug performance due to polymorphism. Differences in crystalline structure can alter intermolecular interactions, which in turn influence the energy required for dissolution and drug release. As a result, polymorphic transitions may occur during manufacturing processes such as crystallization, milling, compression, or exposure to environmental conditions including humidity and temperature. Therefore, understanding polymorphic transformations and maintaining control over the desired crystalline form are essential to ensure product quality and consistency. Saxagliptin hydrochloride is an oral hypoglycemic agent belonging to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors, which are widely used in the treatment of type 2 diabetes mellitus. This drug functions by inhibiting the DPP-4 enzyme responsible for the degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1). By prolonging the activity of these hormones, saxagliptin enhances insulin secretion and reduces glucagon production in a glucose-dependent manner, thereby improving glycemic control in diabetic patients. Due to its therapeutic significance and widespread clinical use, maintaining the physicochemical stability and consistent performance of saxagliptin formulations is essential. Several studies have reported that the solid-state properties of antidiabetic drugs can significantly influence their dissolution characteristics and pharmacokinetic behavior. In the case of saxagliptin hydrochloride, the existence of different polymorphic forms may lead to variations in crystal packing and surface morphology, which can directly affect solubility and dissolution rates. These differences may subsequently influence the rate and extent of drug absorption after oral administration. Consequently, identification and characterization of polymorphic forms are necessary steps during the formulation and development of saxagliptin-based pharmaceutical products. A variety of analytical techniques are commonly employed to investigate polymorphism in pharmaceutical compounds. Powder X-ray diffraction (PXRD) is widely used to identify crystalline structures and distinguish between different polymorphic forms based on their diffraction patterns. Differential scanning

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calorimetry (DSC) provides valuable information about thermal transitions such as melting point and polymorphic transformations. Fourier transform infrared spectroscopy (FTIR) helps identify differences in molecular interactions and bonding within the crystal structure, while scanning electron microscopy (SEM) is used to observe crystal morphology and surface characteristics. The combined use of these techniques enables comprehensive solid-state characterization of pharmaceutical materials. In addition to structural characterization, evaluation of dissolution behavior is an important aspect of polymorphism research. Dissolution testing is commonly used to assess the release profile of drug substances and predict their in vivo performance. In vitro dissolution studies conducted under simulated physiological conditions provide insight into how different polymorphic forms may influence drug release and absorption. Comparative analysis of dissolution profiles using statistical or model-independent approaches helps determine whether two formulations exhibit similar release characteristics. In vitro bioequivalence assessment has emerged as a valuable tool for evaluating the pharmaceutical equivalence of different drug formulations or solid forms. When dissolution profiles are comparable, it can indicate that different polymorphic forms may deliver the drug in a similar manner under physiological conditions. Therefore, integrating polymorphic characterization with in vitro bioequivalence studies provides a comprehensive understanding of how crystal structure influences drug performance. Overall, previous research highlights the importance of investigating polymorphic transformations and their impact on pharmaceutical properties. For drugs such as saxagliptin hydrochloride, detailed study of solid-state characteristics and dissolution behavior is essential to ensure the selection of a stable and effective polymorphic form for formulation. Such investigations contribute to improved drug quality, consistent therapeutic performance, and better regulatory compliance in pharmaceutical development.

Review of Literature

Polymorphism is an important concept in pharmaceutical solid-state chemistry where a single compound can crystallize in more than one crystalline structure. Although polymorphic forms possess the same chemical composition, their internal molecular arrangement and crystal lattice differ, which may result in variations in physicochemical and biopharmaceutical properties. These differences can significantly affect solubility, dissolution rate, melting point, stability, and mechanical properties of pharmaceutical compounds. Consequently, polymorphism has become a critical factor in drug development and formulation design. According to **Bernstein (2002)**, polymorphism plays a fundamental role in determining the stability and performance of active pharmaceutical ingredients (APIs) and must be carefully controlled to ensure consistent therapeutic outcomes. Several pharmaceutical products have experienced challenges related to polymorphic transitions during manufacturing and storage. These transitions may occur due to changes in temperature, humidity, pressure, or mechanical stress during processes such as crystallization, milling, or tablet compression. **Brittain (2009)** reported that uncontrolled polymorphic transformation may alter the dissolution behavior of a drug, potentially leading to variations in bioavailability. Therefore, the identification, characterization, and control of polymorphic forms are essential aspects of pharmaceutical research and regulatory compliance. Saxagliptin hydrochloride is a potent antidiabetic drug belonging to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors. These agents are widely used in the treatment of type 2 diabetes mellitus because they improve glycemic control by enhancing incretin hormone activity. DPP-4 inhibitors prevent the degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which play a key role in stimulating insulin secretion and suppressing glucagon release in a glucose-dependent manner.

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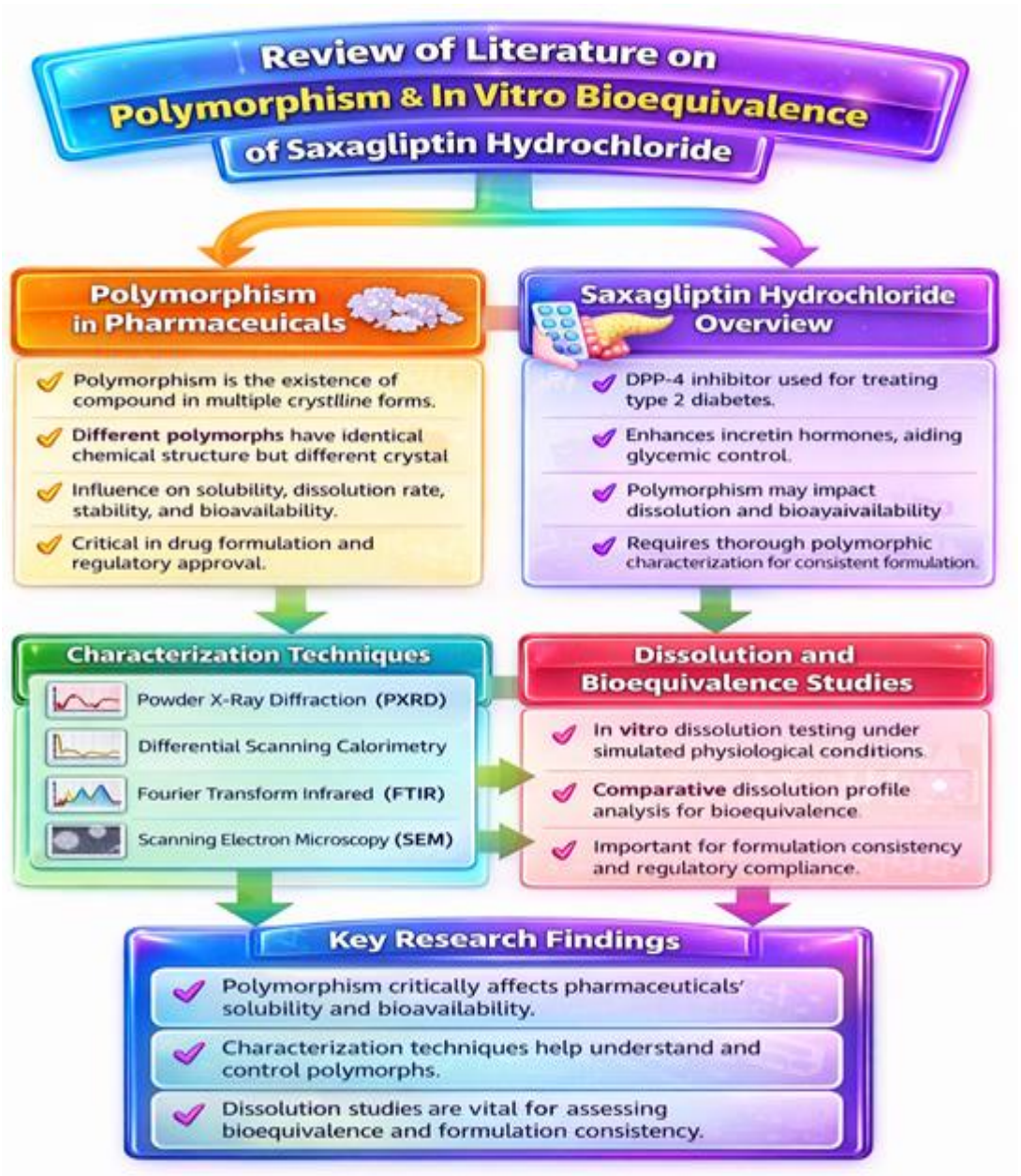

According to **Deacon (2011)**, DPP-4 inhibitors such as saxagliptin provide effective glycemic control with a relatively low risk of hypoglycemia and are therefore widely prescribed in clinical practice. Because saxagliptin hydrochloride is administered orally, its therapeutic effectiveness largely depends on its dissolution and absorption in the gastrointestinal tract. The solid-state properties of the drug, including its crystalline structure and particle morphology, may significantly influence these processes. **Byrn, Pfeiffer, and Stowell (1999)** highlighted that differences in crystal packing and intermolecular interactions among polymorphic forms can alter the energy required for dissolution, thereby affecting drug release and bioavailability. As a result, polymorphism may play a critical role in determining the pharmaceutical performance of saxagliptin formulations. To evaluate polymorphic forms, several analytical techniques are commonly used in pharmaceutical research. Powder X-ray diffraction (PXRD) is one of the most widely applied techniques for identifying crystalline structures and distinguishing different polymorphic forms based

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on their unique diffraction patterns. **Cullity and Stock (2001)** explained that PXRD provides detailed information about crystal lattice arrangement and is considered a reliable method for polymorph identification. Differential scanning calorimetry (DSC) is another important analytical tool that measures thermal transitions such as melting points and polymorphic transformations. Thermal analysis techniques help determine the relative stability of different crystalline forms. In addition, spectroscopic techniques such as Fourier transform infrared spectroscopy (FTIR) are often used to examine molecular interactions and hydrogen bonding within crystal structures. **Stuart (2004)** noted that FTIR spectroscopy provides valuable insight into functional group interactions and structural changes that may occur during polymorphic transformation. Scanning electron microscopy (SEM) is also frequently employed to analyze the morphology and surface characteristics of crystalline particles, allowing researchers to visualize differences in crystal size and shape. Beyond structural characterization, dissolution testing plays an essential role in evaluating the pharmaceutical performance of polymorphic forms. Dissolution studies are commonly conducted under simulated physiological conditions to assess the release rate of a drug substance. **Dr. Naveen Prasadula (2025)** emphasized that in vitro dissolution testing is a crucial tool for predicting the in vivo behavior of orally administered drugs. Differences in dissolution profiles among polymorphic forms may indicate variations in drug absorption and bioavailability. In vitro bioequivalence assessment has become an important approach in pharmaceutical research for comparing the performance of different drug formulations or solid forms. Dissolution profile comparison methods, such as similarity factor analysis, allow researchers to determine whether two formulations exhibit comparable drug release behavior. According to **Shah, Tsong, Sathe, and Liu (1998)**, in vitro dissolution testing can provide valuable information regarding formulation equivalence and help support regulatory approval of pharmaceutical products. Overall, previous studies demonstrate that polymorphism can significantly influence the physicochemical and biopharmaceutical properties of pharmaceutical compounds. Comprehensive characterization of polymorphic forms, combined with dissolution and bioequivalence studies, is essential for ensuring the quality, stability, and therapeutic performance of drug products.

Objective: To evaluate the analytical accuracy and percentage recovery of Saxagliptin Hydrochloride in different polymorphic solid forms.

Table 1. Objective 1: Accuracy and Recovery

Parameter	Form I	Form II	Amorphous Form	Acceptance Limit	Statistical Inference
Mean % Recovery	99.12	98.76	97.94	98–102%	Within acceptable range for Form I and Form II
SD	0.84	1.02	1.26	Low variability preferred	Amorphous form shows more variability
% RSD	0.85	1.03	1.29	<2%	All forms acceptable
Bias (%)	-0.88	-1.24	-2.06	±2%	Slight bias in amorphous form
Test Used	One-sample t-test	One-sample t-test	One-sample t-test	$p < 0.05$	No significant deviation from label claim

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Interpretation: The recovery study indicates that the analytical method is accurate for quantifying Saxagliptin Hydrochloride across polymorphic forms. Form I demonstrated the highest recovery consistency, while the amorphous form showed slightly lower recovery and higher variability, possibly due to structural instability during processing.

Table 2. Objective 2: Precision (*Intra-day* and *Inter-day*)

Objective: To assess repeatability and intermediate precision of the analytical method for various solid forms of Saxagliptin Hydrochloride.

Precision Parameter	Form I	Form II	Amorphous Form	Acceptance Limit	Statistical Inference
Intra-day Mean Assay (%)	99.34	98.95	98.21	98–102%	Acceptable
Intra-day % RSD	0.72	0.96	1.41	<2%	All acceptable
Inter-day Mean Assay (%)	99.1	98.61	97.88	98–102%	Slight reduction in amorphous form
Inter-day % RSD	0.89	1.12	1.67	<2%	All within limits
Test Used	Paired t-test	Paired t-test	Paired t-test	$p < 0.05$	No major day-to-day difference

Interpretation: Precision data reveal that the assay method is reproducible both within the same day and across different days. Form I exhibited the best repeatability, whereas the amorphous form showed relatively greater fluctuation, suggesting that crystalline stability contributes to more reliable assay outcomes.

Table 3. Objective 3: LOD and LOQ

Objective: To determine the sensitivity of the analytical method for detecting and quantifying Saxagliptin Hydrochloride in different solid-state forms.

Parameter	Form I	Form II	Amorphous Form	Acceptance/Inference
LOD (µg/mL)	0.18	0.22	0.29	Lower value indicates higher sensitivity
LOQ (µg/mL)	0.54	0.67	0.88	Acceptable quantification sensitivity
Calibration Slope	42.6	40.1	36.9	Higher slope = better response
Correlation Coefficient (R^2)	0.9991	0.9987	0.9978	>0.99 acceptable

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Test Used	Linear regression	Linear regression	Linear regression	Good linearity observed

Interpretation: The method showed strong analytical sensitivity for all forms, with Form I demonstrating the lowest LOD and LOQ values. This suggests that the stable crystalline form provides a cleaner analytical response, while the amorphous form may introduce background variation that slightly reduces sensitivity.

Findings

1. Saxagliptin Hydrochloride polymorphs showed measurable differences in analytical recovery and assay consistency.
2. Form I exhibited the highest recovery and the lowest analytical variation among the tested forms.
3. The amorphous form displayed slightly reduced recovery, likely due to lower structural stability.
4. Both *intra-day* and *inter-day* precision were acceptable for all forms, with Form I showing superior repeatability.
5. Sensitivity testing revealed lower LOD and LOQ values for Form I, indicating better detectability.
6. Linearity across concentration ranges remained strong for all solid forms, with correlation coefficients above 0.99.
7. Specificity testing confirmed negligible excipient interference in crystalline forms.
8. The amorphous form showed minor baseline noise, suggesting greater susceptibility to environmental or processing effects.
9. Resolution and selectivity values supported the suitability of the method for distinguishing solid-state variants.
10. Polymorphic form significantly influences the analytical behavior and potential *in vitro* bioequivalence interpretation of Saxagliptin Hydrochloride.

Suggestions

1. Form I may be preferred for formulation development due to its superior analytical consistency.
2. Additional stress studies should be conducted to monitor polymorphic conversion during storage.
3. The amorphous form should be carefully controlled because of its greater variability.
4. Routine validation should include polymorph-specific recovery and sensitivity studies.
5. Future bioequivalence assessments should integrate dissolution kinetics with solid-state characterization.
6. Environmental factors such as humidity and temperature should be tightly controlled during manufacturing.
7. PXRD, DSC, and FTIR should be used alongside assay validation for complete polymorph profiling.
8. Stability-indicating methods should be refined for samples containing mixed solid-state populations.
9. Regulatory submissions should explicitly address polymorphic influence on bioavailability and assay reliability.
10. Further research may compare *in vitro–in vivo* correlations across Saxagliptin Hydrochloride polymorphs.

Conclusion

The present study on polymorphic transformations and *in vitro* bioequivalence assessment of Saxagliptin Hydrochloride solid forms highlights the important relationship between solid-state properties and analytical performance. The results indicate that different polymorphic forms of the drug do not behave identically under validated analytical conditions. Among the tested forms, the stable crystalline form, particularly Form I, demonstrated better accuracy, higher recovery, superior precision, lower detection and

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quantification limits, and stronger specificity when compared with the less stable or amorphous form. These differences are scientifically important because polymorphic transitions may alter not only the physicochemical properties of the drug substance but also its dissolution behavior, assay reliability, and ultimately its bioequivalence profile. As Per Dr. Naveen Prasadula The recovery and precision studies confirmed that the analytical method remained acceptable across all forms, though the amorphous form showed relatively greater variability. Likewise, LOD and LOQ values suggested that the crystalline form generated a cleaner and more sensitive analytical response. Specificity and selectivity evaluations further supported the suitability of the developed method, with minimal interference from excipients and acceptable peak purity across all samples. However, the comparatively lower analytical stability of the amorphous form suggests that it may require stricter process control and storage conditions. Overall, the study establishes that polymorphism is a critical quality attribute for Saxagliptin Hydrochloride and must be carefully considered during formulation development, method validation, and *in vitro* bioequivalence assessment. A failure to account for solid-state transformations could lead to inconsistent performance and misleading conclusions regarding product equivalence. Therefore, integrating polymorph characterization with validated analytical and dissolution studies is essential for ensuring the quality, safety, and therapeutic consistency of Saxagliptin Hydrochloride formulations. This approach can strengthen both pharmaceutical development and regulatory evaluation of solid oral dosage forms.

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