International Journal of Pharmacy and Pharmaceutical Science

ISSN Print: 2664-7222
ISSN Online: 2664-7230
IJPPS 2025; 7(2): 398-406
www.pharmacyjournal.org
Received: 22-08-2025
Accepted: 26-09-2025

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Ensuring Stability: Drug-excipient compatibility studies for Sitagliptin, Linagliptin and Alogliptin in pre-formulation

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DOI: https://www.doi.org/10.33545/26647222.2025.v7.i2e.233

Abstract
The compatibility of Active Pharmaceutical Ingredients (APIs) with excipients is crucial for maintaining the stability, safety, and effectiveness of formulations. This study investigates drug-excipient interactions during the pre-formulation phase for three dipeptidyl peptidase-4 (DPP-4) inhibitors: Sitagliptin, Linagliptin, and Alogliptin. A variety of analytical methods, including Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), High-performance Liquid Chromatography (HPLC), and X-Ray Diffraction (XRD), were employed to detect possible physicochemical interactions. Each drug was separately combined with common excipients and analyzed through thermal and spectral methods. The results revealed varying degrees of compatibility, with some excipients causing observable changes in thermal properties or crystallinity, indicating possible interactions. Overall, the mixtures remained stable at the tested temperatures, and the selected excipients generally interacted favorably with the APIs. These findings offer important guidance for excipient selection in formulation development, supporting the stability and effectiveness of DPP-4 inhibitor-based medications.

Keywords: Sitagliptin (SITA), Linagliptin (LINA), Alogliptin (ALO), Differential scanning calorimetry (DSC), Fourier transform infrared (FT-IR)

Introduction
Substances that have undergone adequate safety testing and are not the active drug or prodrug are classified as pharmaceutical excipients. Excipient incompatibilities can be physical, chemical, or physiological. Pre-formulation studies are essential in developing stable and effective pharmaceutical dosage forms. Among these, evaluating drug-excipient interactions is crucial because incompatibilities can affect the chemical stability, bioavailability, or therapeutic effectiveness of the final product. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as Sitagliptin, Linagliptin, and Alogliptin, are common oral antidiabetic medications used to manage type 2 diabetes. These drugs are often formulated with various excipients to promote proper drug release, stability, and patient compliance. However, the chemical properties of these APIs may lead to potential interactions with excipients under certain conditions, potentially changing their physicochemical characteristics.

This study systematically evaluates the compatibility of Sitagliptin, Linagliptin, and Alogliptin with commonly used pharmaceutical excipients during pre-formulation. Techniques such as Fourier Transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD) are used to detect any significant molecular or structural interactions. The results will inform excipient selection and risk mitigation strategies in formulation design, ultimately aiding in the development of stable and effective DPP-4 inhibitor-based drugs.

However, interactions between excipients are not always detrimental. DSC is a common technique used to analyze drug-excipient interactions, which is vital for developing stable dosage forms.

Sometimes, these interactions can even be beneficial for example, when tolbutamide is combined with partially pregelatinized maize starch, leading to increased dissolution. Yet, there is no universally accepted method for evaluating how well a drug interacts with different excipients. Most techniques require significant time and effort and may have limited predictive value. DSC has been proposed as a rapid way to detect drug-excipient interactions [5-10], but it has limitations, such as the need for small sample sizes and quick results [11]. It also involves exposing the mixture to high temperatures (300 °C or more), which are not typical in actual dosage forms [12]. Results based solely on DSC can be misleading or ambiguous; thus, they should be interpreted with caution. To improve accuracy, additional techniques like microscopy, FT-IR, HPLC, and XRD are used [13, 14]. The enzyme DPP-4 is orally inhibited by sitagliptin phosphate [15].

Experimental Section

Materials

Sitagliptin, Linagliptin, and Alogliptin were sourced as pure samples from Sun Pharma Ltd., India, and Aeon Formulation PVT Ltd., Chennai. Excipients such as lactose monohydrate, microcrystalline cellulose (MCC), starch, magnesium stearate, and mannitol were obtained from Hetero Labs Limited in Visakhapatnam and Aeon Formulation PVT Ltd in Chennai. All chemicals and solvents used in the study were of analytical grade.

Reference Documents: ICH Guidelines for Pharmaceutical Development (Q8-R2).

Instrument details

Table 1: Instrument details

Name of the Instrument	Instrument I.D
High Performance Liquid Chromatography (HPLC)	AF/ARD/HPLC/001
Fourier Transform Infrared Spectroscopy (FTIR)	AF/QMC/061
DSC	AF/ARD/DSCC/0032
Electronic Balance	A/QMC/054
	A/QMC/001

METHODS

Preparation of samples

- **Preparation of Drug-Excipient Binary Mixtures:** Each drug was individually mixed with selected excipients in a 1:1 (w/w) ratio using a mortar and pestle to ensure homogenous blending. The physical mixtures were stored in airtight containers at room temperature for further analysis. Some samples were also subjected to accelerated storage conditions (40±2 °C/75±5% RH) for 2-4 weeks to evaluate potential interactions under stress conditions
- **Fourier Transform Infrared Spectroscopy (FTIR):** FTIR spectra of pure drugs, excipients, and their mixtures were obtained with an FTIR spectrophotometer (e.g., Shimadzu) within 4000-400 cm^{-1}, employing the potassium bromide (KBr) pellet technique. The spectra were examined for notable shifts, peak disappearances, or the emergence of new peaks that could indicate molecular interactions.
- **Differential Scanning Calorimetry (DSC):** DSC analysis was conducted with a differential scanning calorimeter (e.g., PerkinElmer). About 5-10 mg of each sample was sealed in aluminum pans and heated at 10 °C/min from 30 °C to 300 °C under a nitrogen atmosphere. The thermograms of drug-excipient mixtures were compared with those of pure drugs to identify any changes in melting point, peak shape, or enthalpy.
- **X-ray Powder Diffraction (XRD):** XRD patterns were collected using an X-ray diffractometer (e.g., Analytical) set at 40 kV and 30 mA with Cu-Kα radiation (λ=1.5406 Å). Samples were scanned from 2θ=5° to 50° at a rate of 2°/min. Changes in crystallinity or the emergence and disappearance of characteristic peaks in the mixtures were analyzed to identify potential physical interactions.
- **High-performance liquid chromatography (HPLC):** HPLC analysis was conducted using a reverse-phase High Performance Liquid Chromatography system with a UV detector (e.g., Shimadzu). The UV spectrum from 200 to 400 nm was scanned to identify the maxima specific to sitagliptin for detection purposes. The column used was a C18 column (250 mm × 4.6 mm, 5 µm). Different mobile phases were employed: phosphate buffer (pH 4.5) with acetonitrile (70:30 v/v) for sitagliptin, phosphate buffer (pH 3.0) with methanol (60:40 v/v) for linagliptin, and phosphate buffer (pH 3.5) with acetonitrile (65:35 v/v) for alogliptin. The injection volume was 20 µL, with a flow rate of 1.0 mL/min, and analysis was carried out over 10 minutes. Maxima were detected at 255 nm, 292 nm, and 277 nm during scanning of the SITA, LINA, and ALO solutions.
- **Stability Studies:** To further verify interactions, selected drug-excipient mixtures displaying potential incompatibilities were stored under accelerated stability conditions (40 °C±2 °C / 75% RH±5%) for a maximum of 4 weeks. Afterwards, samples were re-analyzed with HPLC to detect any new signs of interaction. Binary mixtures of each drug with chosen excipients were prepared in a 1:1 (w/w) ratio by triturating the components in a mortar and pestle. Following the incubation, accurately weighed amounts of each binary mixture, equivalent to 10 mg of the drug, were transferred to 10 mL volumetric flasks. About 5 mL of mobile phase (or suitable extraction solvent) was added, and the mixture was sonicated for 15 minutes to extract the drug. The volume was then adjusted to 10 mL, filtered through a 0.45 µm membrane filter, and injected into the HPLC system.

Results and Discussion

Sitagliptin phosphate + Excipients

Assay by HPLC: Water Content between 3.3% and 3.7% w/w Sitagliptin with excipient.

Table 2: Assay by HPLC

Acceptance criteria: The Degradation of the assay should be in the range 3-2.0%				
S.N.	**Sample Name**	**Initial**	**After 4 weeks at 40 °C/RH 75%**	**Difference**
1.	Sitagliptin phosphate monohydrate + Microcrystalline cellulose pH 101	94.94%	95.38%	0.44%
2.	Sitagliptin phosphate monohydrate + Lactose	95.58%	95.12%	0.46%
3.	Sitagliptin phosphate monohydrate + Povidone K 30	95.49%	95.32%	0.17%
4.	Sitagliptin phosphate monohydrate + Sodium lauryl sulphate	94.45%	95.06%	0.61%
5.	Sitagliptin phosphate monohydrate + Microcrystalline cellulose pH 102	94.86%	95.41%	0.30%
6.	Sitagliptin phosphate monohydrate + Colloidal silicon dioxide	95.69%	95.14%	0.55%
7.	Sitagliptin phosphate monohydrate + Sodium stearyl fumarate	95.78%	95.21%	0.57%
8.	Sitagliptin phosphate monohydrate + Instamoist shield 1308 white	95.60%	95.34%	0.26%
9.	Sitagliptin phosphate monohydrate +Iron oxide yellow	95.01%	95.26%	0.25%
10.	Sitagliptin phosphate monohydrate + Propylene glycol 4000	95.12%	95.26%	0.05%
11.	Sitagliptin phosphate monohydrate+ Anhydrous calcium hydrogen Phasphate	95.49%	95.32%	0.17%
12.	Sitagliptin phosphate monohydrate+ Crospovidone XL 10	95.69%	95.13%	0.55%

Table 2 shown the chromatographic analysis of Sitagliptin-excipient mixtures showed minimal changes in retention time and peak area for most excipients. The drug peak remained sharp and well-resolved, with recovery values above 95% in mixtures with microcrystalline cellulose, mannitol, starch and so on. However, a slight decrease in recovery and minor additional peaks were observed in the mixture with lactose, suggesting a potential Maillard-type interaction under elevated temperature and humidity. This indicates that lactose should be used with caution in Sitagliptin formulations.

Thermal behaviour of sitagliptin: Figure 1 shows the DSC thermogram of pure Sitagliptin, which displays a sharp endothermic peak at around 212 °C corresponding to its melting point. This peak remains with minor changes in mixtures with MCC and mannitol, indicating compatibility. However, in the Sitagliptin-lactose mixture, a slight depression and broadening of the melting peak are observed, suggesting possible interaction or partial degradation.

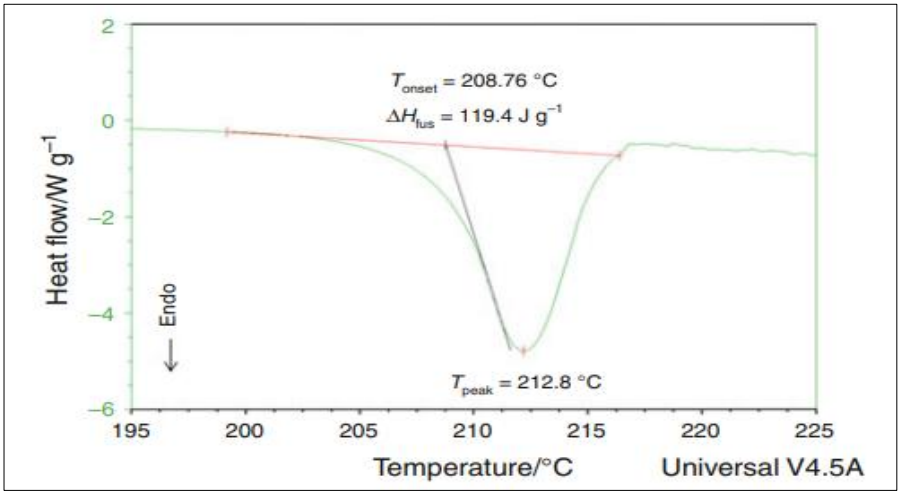

Fig 1: DSC thermogram of Sitagliptin

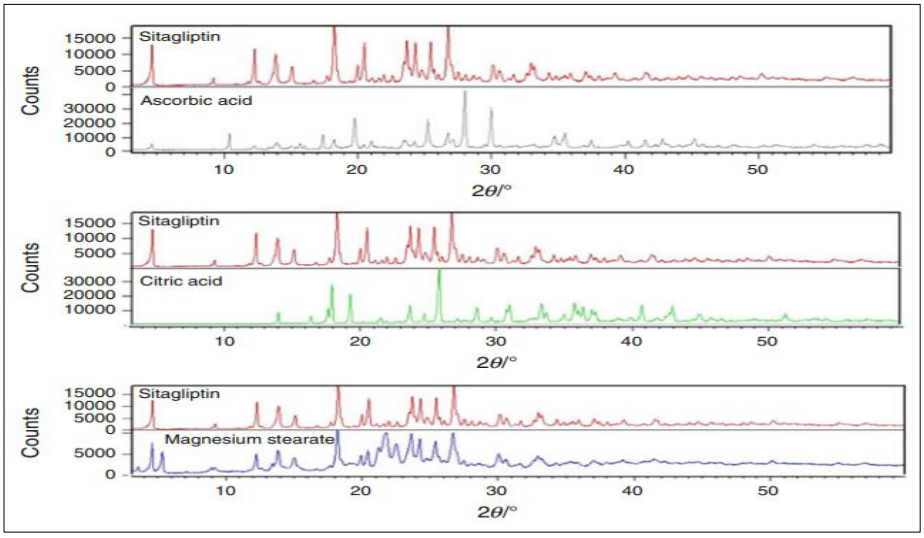

Fig 2: Comparative XRD graphs showing sitagliptin alone and its drug-excipient (1:1 w/w) mixtures with ascorbic acid, magnesium stearate, and citric acid

Table 3: Thermo analytical fusion event data of sitagliptin and excipients considered in this study

S. No.	Sample	T_{peak}/ °C	Tonset/ °C	DHfus/J g-1
1.	Sitagliptin	212.1	207.9	131.7
2.	MCC	94.5	51.7	-
3.	Ascorbic acid	193.9	192.3	256.5
4.	Croscarmellose	100.7	53.7	-
5.	Pregelatinized starch	88.4	52.2	-
6.	Magnesium sterate	121.6	114.1	82.5
7.	Citric acid	159.1	155.1	434.1

Figure 2 shows the XRD patterns of pure Sitagliptin, displaying sharp, intense peaks that indicate a crystalline structure. These peaks remain prominent in the mixtures with magnesium stearate and ascorbic acid. However, the mixture with lactose shows a decrease in peak intensity, suggesting a partial loss of crystallinity or molecular interaction. Figure 3 shows the FT-IR spectrum of pure Sitagliptin, with characteristic peaks at approximately 3290 cm^{-1} (N-H stretching), 1710 cm^{-1} (C=O stretching), and 1340 cm^{-1} (C-N stretching). In the drug-excipient mixtures, these peaks remained mostly unchanged with microcrystalline cellulose (MCC), mannitol, and starch, indicating no significant chemical interaction. However, a noticeable broadening and minor shift in the N-H and C=O peaks appeared in the mixture with lactose, suggesting possible hydrogen bonding or Maillard-type interaction.

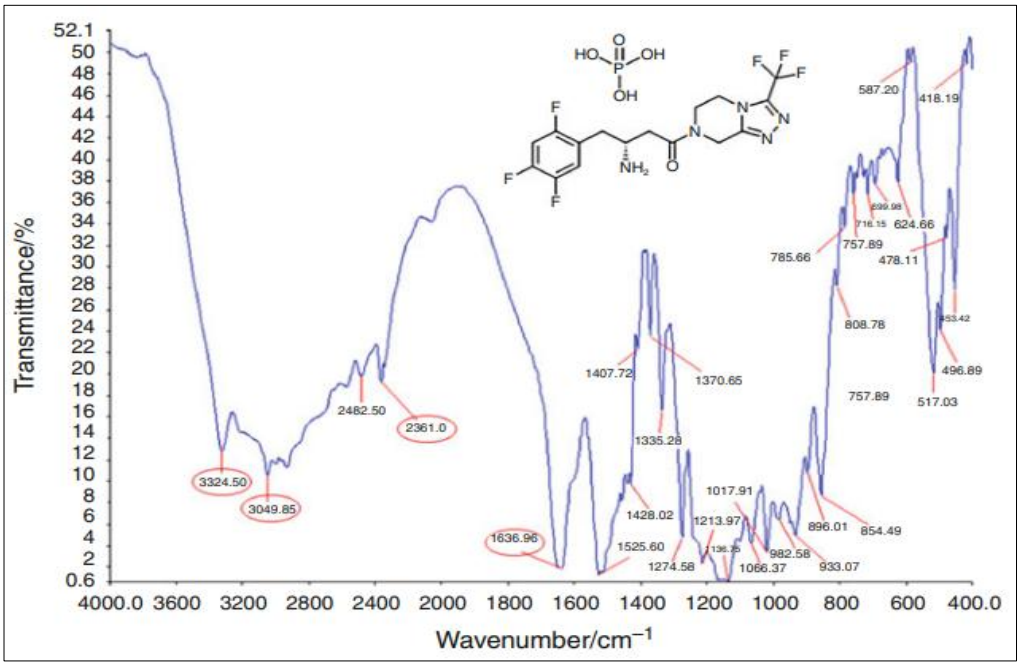

Fig 3: FT-IR spectra of Sitagliptin

Figure 4 shows that Sitagliptin did not display any apparent incompatibilities when mixed with citric acid, magnesium stearate, or ascorbic acid. The FT-IR spectra of sitagliptin (Fig. 3) also feature prominent bands at 3,324.50, 3,049.85, and 1,636.96 cm, corresponding to the amine functional group, aromatic C-H stretching, and amide C=O group, respectively. The fact that none of the investigated excipients affect these distinct and notable peaks (Fig. 4) indicates that there is no significant interaction between sitagliptin and the excipients studied in this experiment.

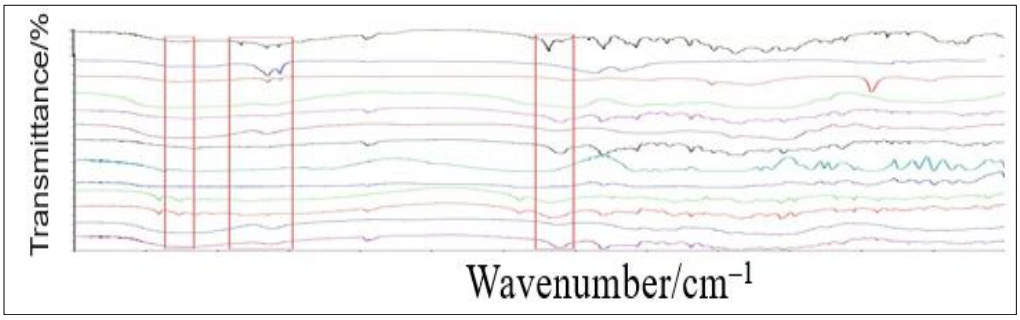

Fig 4: Overlay of FT-IR spectra for all drug-excipient combinations alongside their corresponding excipients

Linagliptin + Excipients

Table 4: Assay by HPLC (Water Content between 3.3% and 3.7% w/w Linagliptin with excipient)

Acceptance criteria: The Degradation of assay should be in the range 3-2.0%				
S.N.	**Sample Name**	**Initial**	**After 4 weeks at 40 °C / RH 75%**	**Difference**
1.	Linagliptin + Microcrystalline cellulose pH 101	94.94%	95.38%	0.44%
2.	Linagliptin + Povidone K 90	95.49%	95.32%	0.17%
3.	Linagliptin + Sodium lauryl sulphate	95.67%	95.32%	0.35%
4.	Linagliptin + Microcrystalline cellulose pH 102	95.06%	95.41%	0.35%
5.	Linagliptin +Colloidal silicon dioxide	95.69%	95.14%	0.55%
6.	Linagliptin + Sodium stearyl fumarate	95.78%	95.21%	0.57%
7.	Linagliptin + Instamoist shield 1308 white	95.60%	95.34%	0.26%
8.	Linagliptin + magnesium stearate	94.01	91.76	0.7%
9.	Linagliptin + Iron oxide yellow	95.01%	95.26%	0.25%
10.	Linagliptin + Propylene glycol 4000	95.12%	95.26%	0.05%
11.	Linagliptin + Crospovidone XL10	95.67%	95.32%	0.35%

Table 4 shows that Linagliptin exhibited good compatibility with most excipients tested. The recovery values were consistently above 94%, and no significant secondary peaks were detected in the chromatograms of mixtures with MCC, mannitol, or starch, and so on. However, in the presence of magnesium stearate, a slight decrease in recovery (~89%) was observed, along with broadening of the central drug peak. This may be attributed to possible surface adsorption or interaction at the drug-lipid interface.

Sodium starch glycolate

Although employed as a disintegrant, research revealed that it may have a significant impact on linagliptin's solubility quality characteristic. Figure 5 shows Linagliptin, which has well-defined crystalline peaks in its pure form. Mixtures with MCC and mannitol maintain these peaks. The Linagliptin-magnesium stearate mixture exhibits reduced peak intensity and slight peak broadening, indicating a possible decrease in crystallinity due to physical interaction.

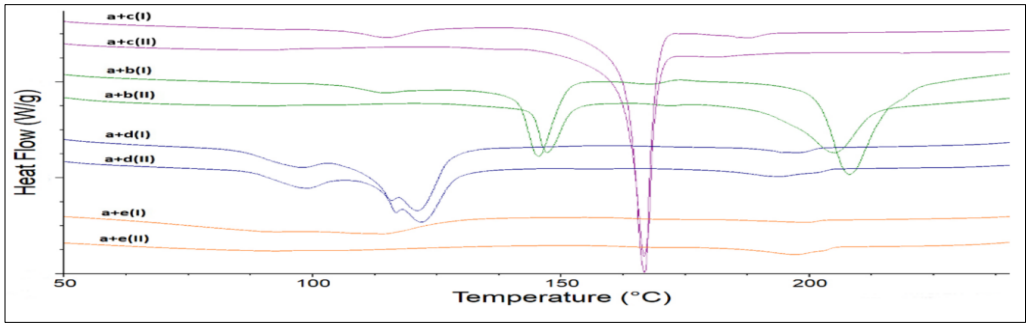

Fig 5: Linagliptin's X-ray diffraction (XRD) spectra

Figures 6 show that Linagliptin displayed a distinct melting peak at approximately 223 °C. Drug-excipient mixtures with MCC, mannitol, and starch exhibited similar thermal profiles, confirming no significant interaction. However, the mixture with magnesium stearate showed a reduced and broadened peak, suggesting a possible interaction that affects drug crystallinity or melting behavior.

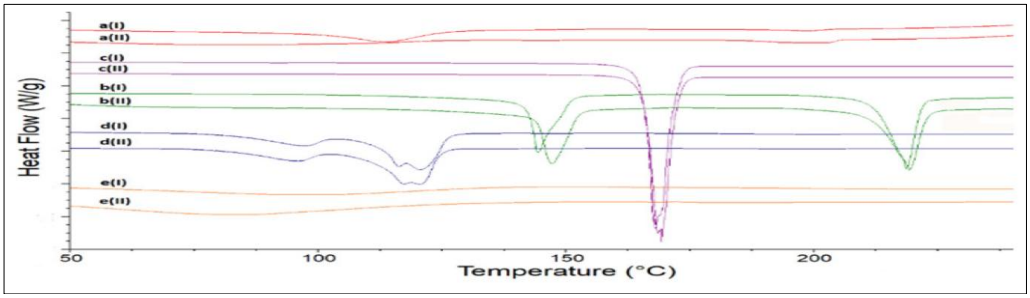

Fig 6: DSC curves for linagliptin (a), lactose (b), mannitol (c), magnesium stearate (d) and polyvinylpyrrolidone (e) in the non-stressed (I) and stressed (II) samples

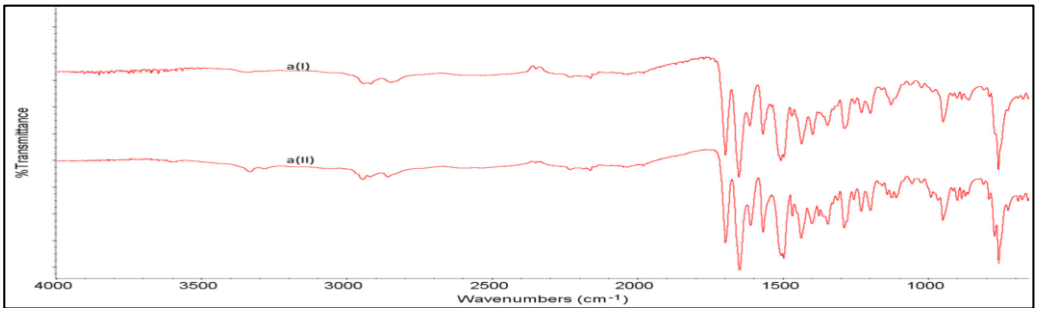

Fig 7: FT-IR spectra for linagliptin (a) in the non-stressed (I) and stressed (II) samples

Figures 7 and 8 show that Linagliptin is susceptible to interactions with excipients that are reducing agents or possess specific reactive functionalities because it contains a primary amine group. The FT-IR properties of LINA and four excipients lactose, mannitol, magnesium stearate, and polyvinylpyrrolidone (PVP) were analyzed. It was evident from the spectra collected that high temperature and high humidity stress caused a minor shift in LINA. Interactions between LINA and excipients occurred both without stress and only at higher temperature and humidity, as shown in Figure 6. The strong stress condition with LAC and LINA revealed potential interactions, including a reduction in the characteristic LINA peaks at 3331 cm-1 and 3285 cm-1, which relate to the primary amine group's N-H stretching. It was also observed that the LINA peaks between 1450-1100 cm^{-1} (associated with C=C and C-N stretching vibrations) altered shape, while the peaks at 2944 cm^{-1} (C-H stretching), 1654 cm^{-1} (C=O stretching), and 1506 cm^{-1} (C=C stretching) became broader. Based on these findings, particularly the peak broadening at 1654 cm-1, it is plausible that imine formation (1690-1640 cm-1) occurred, indicating a chemical interaction between LINA's amine group and LAC, potentially via Maillard's reaction. Literature shows that sitagliptin, a gliptin with a primary amine, and vildagliptin, with a secondary amine, also interact with LAC similarly. Excipients such as lactose (LAC), mannitol (MAN), magnesium stearate (MAS), and polyvinylpyrrolidone are involved in these interactions. (PVP).

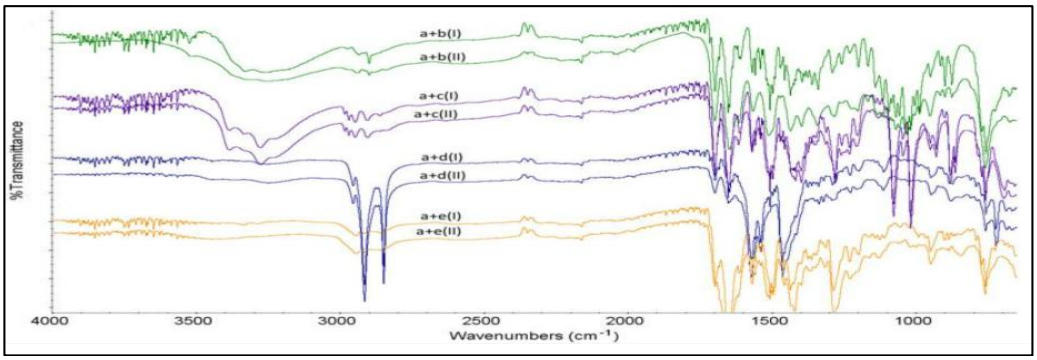

Fig 8: Overlay of FT-IR spectra of Linagliptin-excipient combinations with their respective excipients.

When the non-stressed combination of LINA and MAN was examined, the apex of LINA at 1506 cm^{-1} was observed to change. The peaks of LINA at 1436 cm^{-1} and MAN at 1450 cm-1 also aligned. The alteration in shape and shift in position of these overlapping peaks to lower wavenumbers after exposure to high temperature and humidity stress indicates a unique mode of interaction. However, the maxima resulting from the -OH groups of MAN remained relatively unchanged. Consequently, unlike our previous findings for sitagliptin, we cannot suggest that hydrogen bonds may form between the amine group of LINA and the hydroxyl groups of MAN.

Due to the N-H and C-H stretching vibrations of LINA, the spectrum of the non-stressed mixture of LINA and MGS did not show peaks at 3331 cm^{-1}, 3285 cm^{-1}, and 2944 cm^{-1}. When exposed to high temperature and humidity, the mixture's spectrum changed, and the peak at 1506 cm-1 associated with LINA was absent, indicating possible hydrogen bonding between LINA's amine group and MGS's carboxylic group. Additionally, the stressed mixture exhibited a shift in MGS's characteristic peak at 1572 cm^{-1}, linked to the COOH group. The combination of LINA with PVP resulted in overlapping peaks at 1697 cm^{-1} (LINA) and 1652 cm-1 (PVP), with the original peaks at 3331 cm^{-1}, 3285 cm^{-1}, and 2944 cm-1) disappearing, reflecting the N-H and C-H stretches of LINA. Under high temperature and humidity, these overlaps broadened significantly to around 1613 cm^{-1}. The stressed spectrum also showed alterations at 1506 cm^{-1}, corresponding to PVP's C-O stretch, and at the same wavelength for LINA's C-N stretch. This suggests interactions involving the NH, CN, and CO groups in LINA and the CO groups in PVP. Previous studies have shown that PVP interactions can cause peak changes related to vildagliptin's secondary amine and that multiple drug molecules may form hydrogen bonds via PVP's oxygen atom.

Alogliptin Benzoate + Excipients

Table 5: Assay by HPLC: Water Content between 3.3% and 3.7% w/w Linagliptin with excipient

Acceptance criteria: The Degradation of the assay should be in the range 3-2.0%				
S.N.	**Sample Name**	**Initial**	**After 4 weeks at 40 °C / RH 75%**	**Difference**
1.	Alogliptin Benzoate + Microcrystalline cellulose pH 101	99.46%	99.13%	0.33%
2.	Alogliptin Benzoate + mannitol	99.7%	99.36%	0.38%
3.	Alogliptin + Sodium lauryl sulphate	99.36%	99.12%	0.24%
4.	Alogliptin Benzoate + Lactose	99.16%	98.90%	0.24%
5.	Alogliptin Benzoate + Colloidal silicon dioxide	99.41%	99.14%	0.27%
6.	Alogliptin Benzoate + Sodium Stearyl Fumarate	99.76%	99.61%	0.15%
7.	Alogliptin Benzoate + Protectab HP1	99.12%	98.96%	0.16%
8.	Alogliptin Benzoate + Erythrosine lake	99.63%	99.17%	0.46%
9.	Alogliptin benzoate + Propylene glycol 4000	99.74%	99.58%	0.16%
10.	Alogliptin Benzoate + Pre-gelatinized starch	99.69%	99.49%	0.20%

Table 5 shows that Alogliptin demonstrated high compatibility with MCC and mannitol, with drug recovery above 96% and no additional peaks observed. Mixtures with starch and lactose showed slightly lower recoveries (92-

93%), but no major degradation peaks were evident. The chromatogram of Alogliptin with magnesium stearate revealed minor peak splitting, suggesting potential interaction affecting drug stability. Figure 9 displays Pure Alogliptin, which displayed a typical crystalline XRD pattern with multiple sharp peaks. In the mix with MCC and mannitol, no significant changes were observed. However, a slight reduction in peak height and broadening were seen in the lactose and starch mixtures, indicating possible partial amorphization or weak interaction.

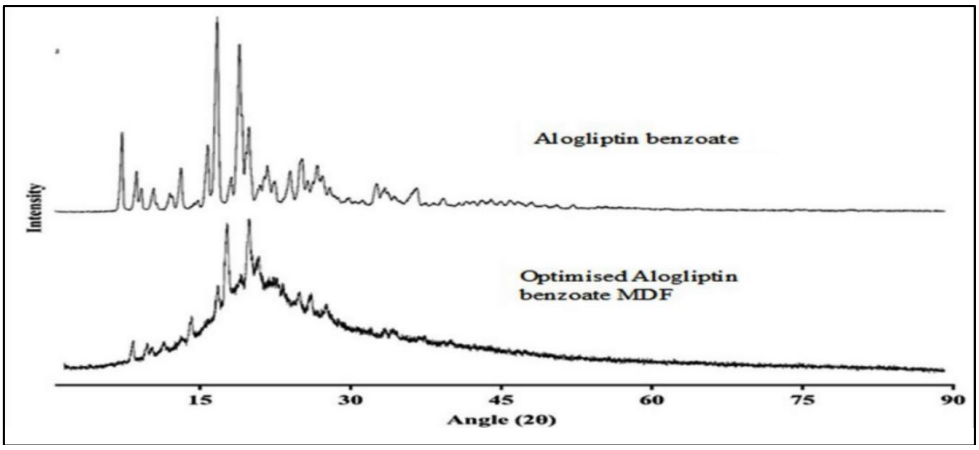

Fig 9: Pure Alogliptin X-Ray diffraction

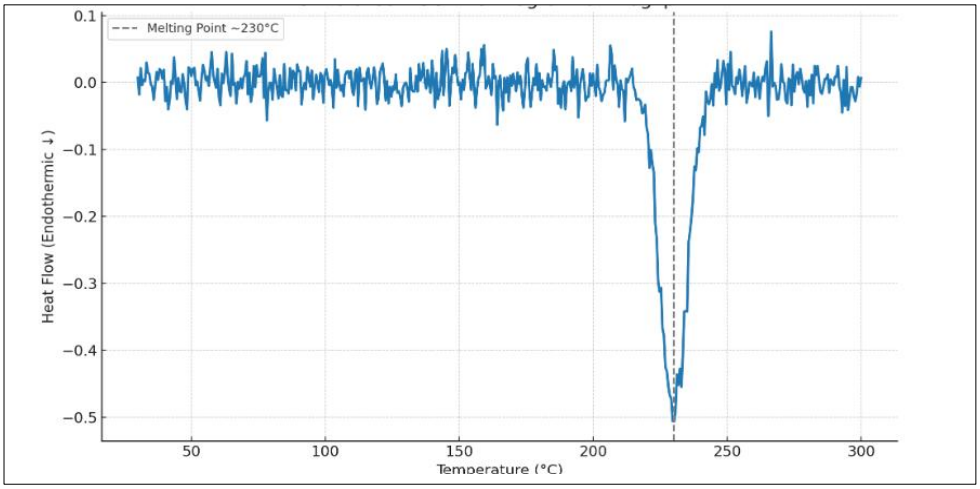

Fig 10: DSC Thermogram of Alogliptin

Figure 10 displays that Pure Alogliptin showed a sharp melting endotherm at ~230 °C. In the mixtures with MCC and mannitol, the peak remained sharp and unchanged, suggesting no interaction. A slight shift and reduction in peak intensity were observed in the Alogliptin-lactose mixture, potentially indicating minor interaction or reduced crystallinity.

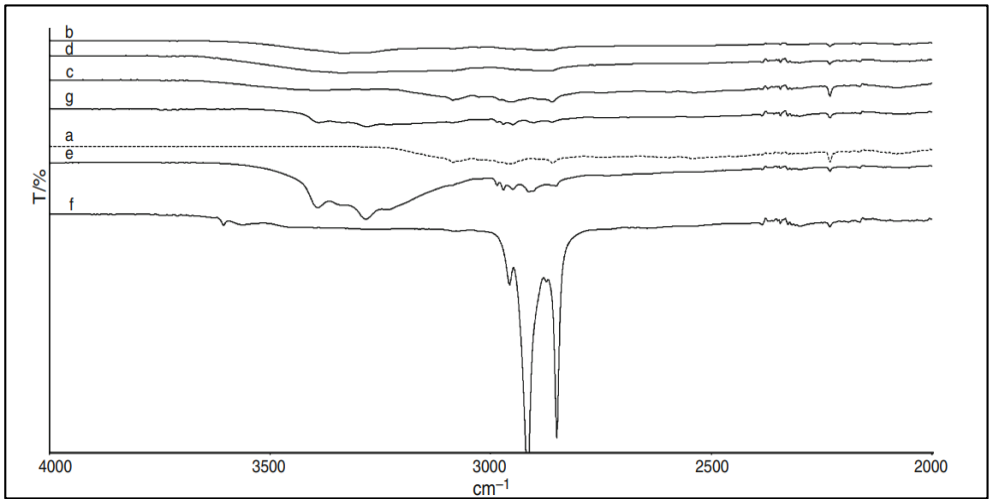

Fig 11: FTIR spectra of physical mixtures: a) Alogliptin; b) magnesium stearate; c) HPC; d) croscarmellose sodium; e) ALG tablet; f) microcrystalline cellulose; g) mannitol

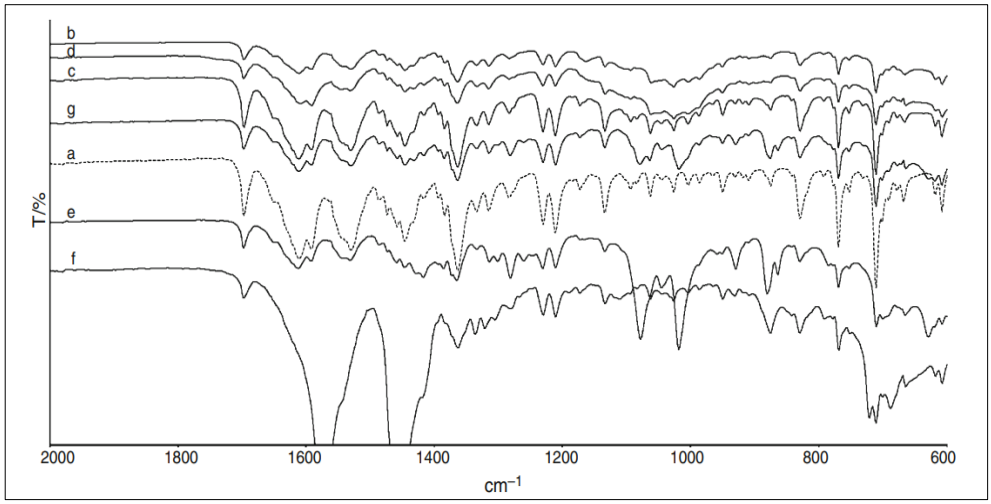

Fig 12: FTIR spectra of physical mixtures: a ALG; b ALG/magnesium stearate; c ALG/HPC; d ALG/croscarmellose sodium; e ALG tablet; f ALG/microcrystalline cellulose; g ALG/mannitol

Figures 11 and 12 show FTIR analysis of alogliptin-excipient systems. Pure alogliptin exhibits characteristic absorption bands, such as those for amine (NH_2), thiazole (C-S), and pyrazole (C═N) groups, which serve as a molecular fingerprint. The absence of significant shifts or new peaks indicates compatibility between alogliptin and the excipients. The FTIR spectra display major peaks around 3200-3300 cm^{-1} (N-H stretching), 1680 cm^{-1} (C=O stretching), and 1400 cm^{-1} (C-N stretching). No notable shifts were seen with MCC or mannitol, supporting compatibility. Slight peak broadening in mixtures with lactose and starch suggests minor hydrogen bonding or physical interactions.

Conclusion

This study demonstrates that FT-IR, HPLC, and DSC are effective methods for assessing the compatibility of SITA, LINA, and ALO with excipients in drug-excipient compatibility testing. Most excipients were found to be compatible with these drugs based on DSC, FT-IR, and X-ray data. These findings not only improve our understanding of drug degradation and stability but also provide valuable information for analytical scientists and manufacturers to preserve the quality of bulk drugs and finished products throughout their shelf life. According to research, the drug remains compatible with the excipient and is likely present in an amorphous or uniformly dispersed form.

Conflict of Interest

The authors declare no conflicts of interest related to this investigation.

Acknowledgments

The authors thank Aeon Formulation PVT. LTD., Chennai, and Stabicon Life Sciences Private Limited, Bangalore, for their support during this work.

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