Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/8d6dhn24

# FORMULATION DEVELOPMENT AND CHARACTERIZATION OF MULTIPLE LAYER TABLETS OF IMMEDIATE RELEASE SITAGLIPTIN AND EXTENDED RELEASE METFORMIN

**Abdullah Diyo[1], Muhammad Ali Ghoto[2], Mah'd Musa Eid Abu Dhair[3], Rabia Mangi[4], Waqar Ahmed[5]**

[1-5]Department of Pharmacy Practice, Faculty of Pharmacy, University of Sindh, Jamshoro, Pakistan

***Corresponding author:** Prof. Dr. Mohammad Ali Ghoto,
*Department of Pharmacy Practice, Faculty of Pharmacy, University of Sindh, Jamshoro, Pakistan.
Email: mali.ghoto@usindh.edu.pk

## ABSTRACT

The management of type 2 diabetes mellitus often necessitates combination therapy, which can increase treatment complexity and reduce patient compliance. Fixed-dose combination (FDC) tablets of sitagliptin and metformin offer a practical solution but are often associated with high production costs and formulation challenges. This study aimed to develop cost-effective multilayer tablets combining immediate-release (IR) sitagliptin and sustained-release (SR) metformin, and to evaluate final product performance in terms of critical parameters.

Six formulations were prepared, four bilayer and two trilayer tablets using wet granulation and direct compression techniques. Pre-formulation studies confirmed satisfactory flow and compressibility. All formulations passed standard physical and chemical quality tests. Sitagliptin showed >85% release within 30 minutes, meeting IR criteria. Metformin release was sustained over 12 hours, with trilayer formulations (F5, F6) closely matching the reference product, *Janumet XR®*.

Comparative dissolution testing using model-independent ($f1$ and $f2$) and model-dependent (zero-order, Higuchi, and Korsmeyer–Peppas) approaches identified F1, F5, and F6 as pharmaceutically equivalent to the innovator product. These formulations followed zero-order release kinetics and anomalous non-Fickian diffusion, indicating controlled and predictable drug release. Stability testing under ICH conditions demonstrated no significant changes in drug content or dissolution behavior over six months.

In conclusion, the optimized multilayer tablet formulations (F1, F5, F6) offer a robust, scalable alternative to existing FDC products, with potential for local use and export market.

**Key words:** Sitagliptin, Metformin, Fixed-dose combination, Pre-formulation, Dissolution, Stability

## INTRODUCTION

Diabetes mellitus (DM) is a combination of metabolic disorders characterized by chronic hyperglycemia (high blood glucose level), due to defects in insulin action and/or insulin secretion (Sarkar et al., 2019; Tripathi & Srivastava, 2006). Low levels of insulin to attain acceptable response and/or resistance of the target tissues to insulin, mainly adipose tissue, skeletal muscles, and (to a lesser extent) liver at the level of insulin receptors, signal transduction system, and/or effector enzymes are the responsible factor for such metabolic abnormalities (Petersen & Shulman, 2018).

Pharmacological intervention is typically required alongside lifestyle modification. Among available therapies, metformin, a biguanide, remains the first-line agent due to its glucose-lowering efficacy and safety profile. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, complement metformin by enhancing incretin activity, thereby improving insulin secretion and glycemic control without significant risk of hypoglycemia or weight gain. Combining these two agents in a single formulation aligns with current therapeutic guidelines, which increasingly recommend early use of combination therapy to improve outcomes and reduce complications. Fixed-dose combinations (FDCs) not only enhance patient compliance by simplifying regimens but also reduce pill burden and treatment costs in the long run (Jha et al., 2023).

Despite the availability of FDC products such as Janumet XR®, current manufacturing technologies especially those employing layered coating of sitagliptin over metformin cores pose several practical and technical limitations including variable drug release profiles and content uniformity, Instability of sitagliptin in coated forms over time and high production costs due to advanced manufacturing processes (Kant et al., 2024).

Moreover, prior research has not comprehensively addressed the pre-formulation compatibility of sitagliptin and metformin with different excipients and polymers, nor established pharmaceutical equivalency to reference products using both model-dependent and model-independent dissolution analyses. Thus, there is a clear need for a cost-effective, technically simpler, and regulatory-compliant formulation approach to produce a stable and efficacious multilayer tablet of these agents (Kelleher et al., 2019).

This study was aimed to develop multilayer (bilayer and trilayer) tablets containing immediate-release sitagliptin and sustained-release metformin to overcome the limitations of current FDC products.

## METHODS

Sitagliptin phosphate monohydrate and metformin hydrochloride were obtained from Hilton Pharmaceuticals, Karachi, along with certificates of analysis. All excipients used were of pharmaceutical grade.

### *Pre-formulation Studies*

Identification of the APIs was confirmed by melting point, UV spectroscopy, HPLC retention time, and FTIR analysis. Bulk and tapped densities, angle of repose, Hausner ratio, and Carr's compressibility index were assessed to evaluate flow properties and compressibility of powders. Drug-excipient compatibility was assessed using literature data and FTIR.

### *Formulation Development*

Bilayer and trilayer tablets containing immediate-release (IR) sitagliptin and sustained-release (SR) metformin were formulated using wet granulation. Granules were prepared separately for both drugs and compressed using a ZP-23 double-hopper bilayer tablet press machine. In bilayer tablets, SR metformin was compressed first, followed by IR sitagliptin. In trilayer tablets, two SR metformin layers (250 mg each) were compressed sequentially before the IR sitagliptin layer. All formulations were coated using a Thiocota machine. A total of six formulations were developed: four bilayer (F1–F4) and two trilayer tablets (F5–F6), varying in polymer combinations for metformin's SR matrix.

### *Evaluation of Tablets*

All formulations underwent standard physical tests including weight variation, thickness, hardness, and friability as per USP (Pharmacopeia, 2016). Assays of both APIs were performed using validated HPLC methods with UV detection (sitagliptin at 205 nm, metformin at 218 nm), and system suitability criteria were applied.

***In Vitro Dissolution Studies***

Dissolution studies were conducted using USP Type II apparatus at 37°C and 50 rpm. A two-stage dissolution medium was used: 0.1N HCl (pH 1.2) for 2 hours followed by phosphate buffer (pH 6.8). Sitagliptin release was monitored over 45 minutes, while metformin release was monitored up to 12 hours. Drug concentrations were determined via UV spectrophotometry (267 nm for sitagliptin, 231 nm for metformin).

***Comparative Dissolution Profile***

Comparative dissolution profiles were evaluated against the reference product (Janumet XR®) using both model-independent ($f1$ and $f2$ factors) and model-dependent (zero-order, first-order, Higuchi, and Korsmeyer–Peppas) approaches. Values of $f1$ between 0–15 and $f2$ between 50-100 were considered indicative of similarity.

***Stability Studies***

Stability studies were conducted under ICH Zone IV-A conditions (40°C ± 2°C / 75% ± 5% RH) to evaluate the stability of the optimized formulations over time.

**RESULTS**

***Pre-formulation Studies***

Both sitagliptin phosphate and metformin HCl were identified via melting point (216°C and 218°C, respectively), UV spectra (λmax at 267 nm and 231 nm), HPLC retention time, and FTIR analysis (Figures 1 and 2). Powder flow and compressibility characteristics such as bulk/tapped densities, angle of repose, Hausner ratio, and Carr's index indicated acceptable flow properties, suitable for direct compression or wet granulation.

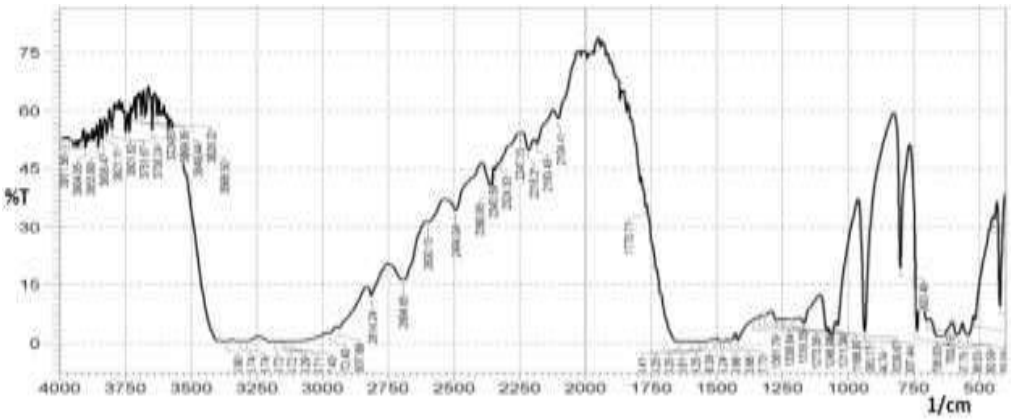



**Figure 1: IR Spectrum of sitagliptin phosphate drug**

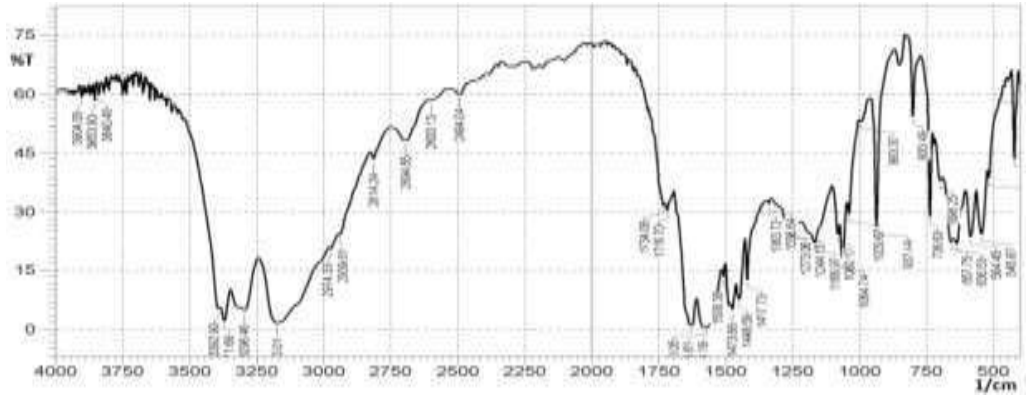



**Figure 2: IR Spectrum of metformin HCl drug**

***Physicochemical tests***

All six formulations (F1-F6) exhibited uniform physical characteristics. Average tablet weights were within acceptable variation limits (875–935 mg), hardness ranged between 9.6 and 13.8 kg/cm², thickness 2.1-2.9 mm, and friability <0.25%. Assay results demonstrated sitagliptin content between 98.8%–101.2% and metformin content between 99.2%–103.05% for both coated and uncoated tablets, ensuring dose accuracy and compliance with pharmacopeial standards. Dissolution studies revealed that Sitagliptin IR layer released >85% within 30 minutes in all formulations, with F6 achieving 101%. Metformin SR release varied depending on polymer combination with F3 and F4 showing less than 80% drug release after 10 hours. (Table 1)

**Table 1: Results of physicochemical tests of formulations**

| **Test** | | **Formulation** | | | | | |
|---|---|---|---|---|---|---|---|
| | | Bilayer | | | | Tri-layer | |
| | | F1 | F2 | F3 | F4 | F5 | F6 |
| Weight Variation (mg) (n=20) | | 931 ± 6 | 879 ± 6 | 928 ± 6 | 935 ± 7 | 899 ± 7 | 932 ± 6 |
| Hardness (kg/cm$^2$) (n=3) | | 10.1 | 10.2 | 10.2 | 10.9 | 13.8 | 13.6 |
| Thickness (mm) (n=3) | | 2.2 | 2.2 | 2.3 | 2.3 | 2.9 | 2.9 |
| Friability % (n=20) | | 0.13 | 0.14 | 0.15 | 0.14 | 0.17 | 0.18 |
| Assay (%) (n=6) | sitagliptin | 99.7 | 101.20 | 98.9 | 99.3 | 101.1 | 100.98 |
| | Metformin | 101.9 | 102.1 | 101 | 99.4 | 101.95 | 103.05 |
| Dissolution (%) (Sitagliptin) | 30 min | 98.8 | 101 | 84.8 | 88.2 | 98.4 | 101 |
| Dissolution (%) Metformin | 1 h | 25.4 | 36.5 | 9.2 | 8.4 | 30.1 | 29.2 |
| | 3 h | 50.2 | 59.8 | 14.3 | 16.2 | 55.6 | 59.1 |
| | 10 h | 89.6 | 90.2 | 48.2 | 56.3 | 89.7 | 89.9 |

***Drug release studies***

***Model Independent Approach***

All formulations were evaluated over 45 minutes for sitagliptin and over 12 hours for metformin along with the reference product Janumet XR. All formulations show more than 85% release after 45 minutes however drug release of F3 and F4 was less than 75% after 30 minutes although the reference product show >75% drug release within 15 minutes. Formulation F1, F5 and F6 shows comparable drug release as compared to the reference product while F3 and F4 shows significantly low drug release. Using model-independent methods ($f1$ and $f2$), formulations F1, F5, and F6 showed high similarity to Janumet XR. For sitagliptin, $f2$ values were above 50 for these formulations (Table 4). For metformin, only F1, F5, and F6 met the similarity threshold ($f2 > 50$), indicating comparable release kinetics (Table 2 and 3 and Figure 3,4).

**Table 2: Cumulative % drug release and *f*1 and *f*2 values for Sitagliptin**

| **Time (min)** | **Cumulative sitagliptin release (%)** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Janumet XR** | **F1** | **F2** | **F3** | **F4** | F5 | **F6** |
| 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 5 | 29.7 | 19.4 | 33.5 | 18.7 | 15.4 | 25.7 | 31.3 |
| 10 | 50.2 | 55.6 | 64.1 | 41.6 | 37.8 | 54.8 | 59.7 |
| 15 | 75.4 | 72.3 | 79.4 | 59.4 | 55.2 | 77.6 | 80.2 |
| 30 | 87.2 | 85.6 | 90.2 | 71.6 | 70.9 | 85.2 | 91.4 |
| 45 | 95.4 | 98.8 | 100.7 | 84.8 | 88.2 | 98.4 | 100.7 |
| ***f*1 (0-15)** | | **7.04** | **8.88** | 18.29 | 20.83 | **4.68** | **7.52** |
| ***f*2 (50-100)** | | **64.02** | **58.80** | 46.71 | 43.52 | **74.82** | **63.85** |

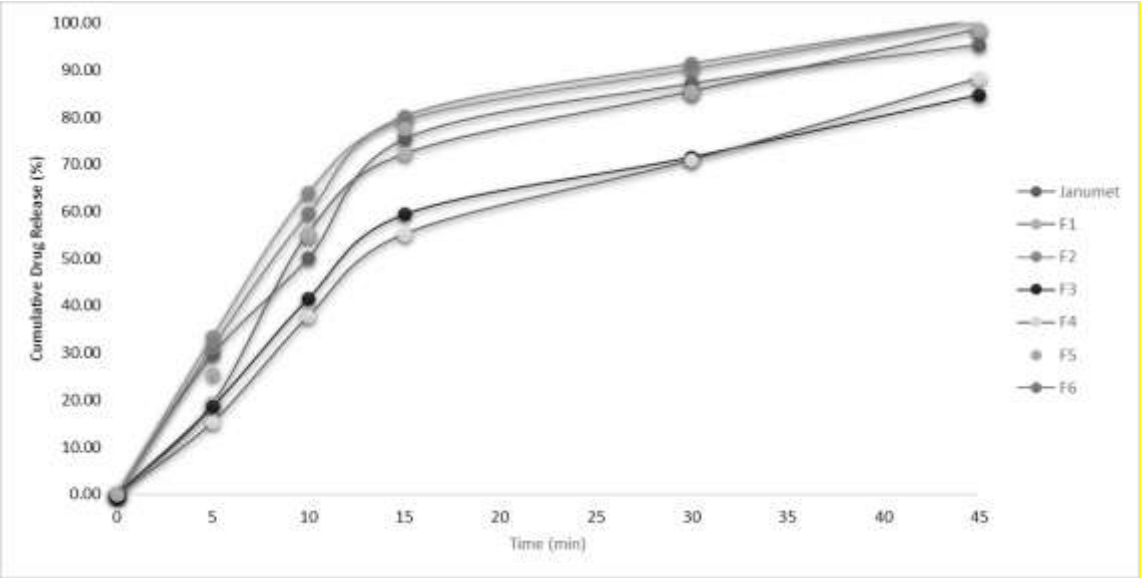
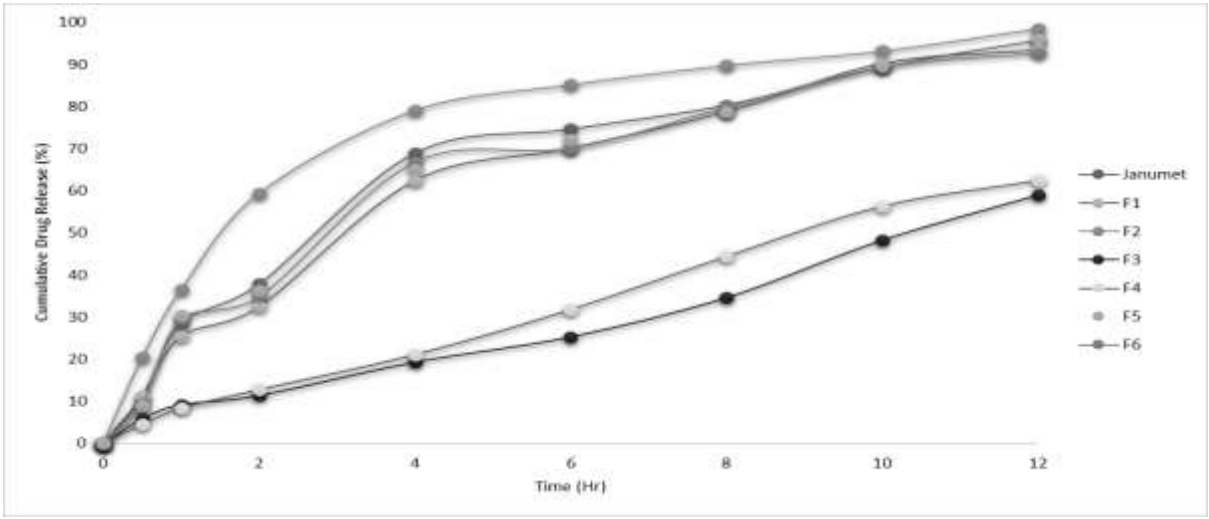



**Figure 3: Cumulative percent of sitagliptin release of all formulations in comparison to Janumet XR.**

**Table 3: Cumulative % drug release and *f*1 and *f*2 values for Metformin**

| Time (h) | Cumulative metformin HCl release (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Janumet XR** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 0.5 | 10.6 | 11.3 | 20.4 | 5.9 | 4.6 | 8.9 | 9.4 |
| 1 | 28.5 | 25.5 | 36.5 | 9.2 | 8.4 | 30.5 | 29.6 |
| 2 | 37.8 | 32.5 | 59.4 | 11.4 | 12.8 | 36.3 | 34.9 |
| 4 | 68.9 | 62.4 | 79.1 | 19.3 | 21.1 | 65.2 | 66.8 |
| 6 | 74.6 | 70.1 | 85.2 | 25.3 | 31.8 | 72.2 | 70.1 |
| 8 | 80.3 | 78.8 | 89.8 | 34.6 | 44.4 | 78.7 | 79.8 |
| 10 | 89.3 | 90.2 | 93.2 | 48.2 | 56.3 | 89.9 | 89.4 |
| 12 | 95.7 | 93.4 | 98.5 | 58.9 | 62.4 | 95.9 | 92.7 |
| ***f*1 (0-15)** | | **5.09** | 15.73 | 56.19 | 50.22 | **2.82** | **3.17** |
| ***f*2 (50-100)** | | **72.11** | 49.24 | 22.70 | 25.40 | **83.66** | **80.55** |




**`Figure 4: Cumulative percent of metformin release of all formulations in comparison to Janumet XR**

***Model Dependent Approach***

Data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Formulations F1, F5, F6, and Janumet XR followed zero-order and Korsmeyer–Peppas release ($R^2 > 0.99$), suggesting controlled matrix diffusion (Table 4)

**Table 4: Regression coefficients ($R^2$) and diffusion exponent (n) from drug release models.**

| Model | | Formulation | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Janumet XR | F1 | F2 | F3 | F4 | F5 | F6 |
| Zero order | R2 | 0.990 | 0.996 | 0.806 | 0.983 | 0.995 | 0.993 | 0.992 |
| First order | R2 | 0.893 | 0.919 | 0.972 | 0.945 | 0.982 | 0.9 | 0.944 |
| Higuchi | R2 | 0.983 | 0.979 | 0.916 | 0.918 | 0.962 | 0.991 | 0.990 |
| Korsmeyer-Peppas model | R2 | 0.986 | 0.989 | 0.999 | 0.965 | 0.991 | 0.996 | 0.995 |
| | n | 0.93 | 0.83 | 1.01 | 0.69 | 0.81 | 0.73 | 0.78 |

***Stability Studies***

Accelerated (40°C/75% RH) and real-time (30°C/65% RH) studies over 6 months showed no significant change in physical parameters, drug content, or dissolution behavior. All formulations remained within ICH acceptance criteria (Table 5).

**Table 5: Results of stability studies for the developed formulations.**

| **Test** | | **Acceptance criteria** | **Formulation F1** | | | | |
|---|---|---|---|---|---|---|---|
| | | | **Initial** | **3 Months** | | **6 Months** | |
| | | | | **Accelerated** | **Real time** | **Accelerated** | **Real time** |
| **Dissolution** | Sitagliptin | NLT 75% (Q) in 30 min | 98.8 | 97.4 | 98.5 | 97.1 | 98.2 |
| | Metformin (1hr) | 22 – 42 % | 25.4 | 24.7 | 25.1 | 24.5 | 24.8 |
| | Metformin (3hr) | 49 – 69 % | 50.2 | 50.3 | 50.5 | 51.5 | 51.6 |
| | Metformin (10hr) | NLT 85% | 89.6 | 89.2 | 89.4 | 89.3 | 90.2 |
| **Assay** | Sitagliptin | 90 – 110 % | 99.7 | 99.4 | 99.5 | 99.1 | 99.2 |
| | Metformin | 90 – 110 % | 101.90 | 101.65 | 101.77 | 101.43 | 101.61 |
| **Formulation F2** | | | | | | | |
| **Dissolution** | Sitagliptin | NLT 75% (Q) in 30 min | 101 | 100.78 | 100.95 | 100.46 | 100.91 |
| | Metformin (1hr) | 22 – 42 % | 36.5 | 34.2 | 35.3 | 34.7 | 34.9 |
| | Metformin (3hr) | 49 – 69 % | 59.8 | 58.6 | 59.2 | 58.1 | 58.7 |
| | Metformin (10hr) | NLT 85% | 90.2 | 89.6 | 89.9 | 89.4 | 89.8 |
| **Assay** | Sitagliptin | 90 – 110 % | 101.20 | 101.04 | 101.14 | 100.95 | 101.09 |
| | Metformin | 90 – 110 % | 102.10 | 101.96 | 102.02 | 101.83 | 101.97 |
| **Formulation F3** | | | | | | | |
| **Dissolution** | Sitagliptin | NLT 75% (Q) in 30 min | 84.8 | 84.1 | 84.4 | 83.6 | 84.2 |
| | Metformin (1hr) | 22 – 42 % | 9.2 | 8.8 | 8.9 | 8.3 | 8.6 |
| | Metformin (3hr) | 49 – 69 % | 14.3 | 13.9 | 14.1 | 13.5 | 13.7 |
| | Metformin (10hr) | NLT 85% | 48.2 | 47.8 | 47.9 | 47.3 | 47.6 |
| **Assay** | Sitagliptin | 90 – 110 % | 98.9 | 98.3 | 98.5 | 97.8 | 98.2 |
| | Metformin | 90 – 110 % | 101.0 | 100.87 | 100.93 | 100.81 | 100.88 |
| **Formulation F4** | | | | | | | |
| **Dissolution** | Sitagliptin | NLT 75% (Q) in 30 min | 88.2 | 87.6 | 87.9 | 87.2 | 87.7 |
| | Metformin (1hr) | 22 – 42 % | 8.4 | 8.1 | 8.2 | 7.6 | 7.9 |
| | Metformin (3hr) | 49 – 69 % | 16.2 | 15.6 | 15.8 | 15.1 | 15.5 |
| | Metformin (10hr) | NLT 85% | 56.3 | 55.7 | 55.9 | 55.1 | 55.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Assay** | Sitagliptin | 90 – 110 % | 99.3 | 98.6 | 98.8 | 98.2 | 98.6 |
| | Metformin | 90 – 110 % | 99.4 | 98.7 | 99.1 | 98.0 | 98.7 |
| **Formulation F5** | | | | | | | |
| **Dissolution** | Sitagliptin | NLT 75% (Q) in 30 min | 98.4 | 97.8 | 98.0 | 97.3 | 97.7 |
| | Metformin (1hr) | 22 – 42 % | 30.1 | 31.3 | 30.5 | 30.5 | 30.2 |
| | Metformin (3hr) | 49 – 69 % | 55.6 | 54.9 | 55.2 | 54.4 | 54.7 |
| | Metformin (10hr) | NLT 85% | 89.7 | 89.2 | 89.3 | 89.5 | 89.4 |
| **Assay** | Sitagliptin | 90 – 110 % | 101.10 | 100.97 | 101.03 | 100.88 | 100.98 |
| | Metformin | 90 – 110 % | 101.95 | 101.91 | 101.94 | 101.83 | 101.91 |
| **Formulation F6** | | | | | | | |
| **Dissolution** | Sitagliptin | NLT 75% (Q) in 30 min | 101 | 100.95 | 100.97 | 100.89 | 100.93 |
| | Metformin (1hr) | 22 – 42 % | 29.2 | 29.5 | 29.4 | 29.8 | 28.7 |
| | Metformin (3hr) | 49 – 69 % | 59.1 | 58.6 | 58.9 | 58.2 | 58.1 |
| | Metformin (10hr) | NLT 85% | 89.9 | 89.4 | 89.6 | 88.7 | 89.2 |
| **Assay** | Sitagliptin | 90 – 110 % | 100.98 | 100.91 | 100.94 | 100.83 | 100.90 |
| | Metformin | 90 – 110 % | 103.05 | 102.98 | 103.0 | 102.91 | 102.96 |

## DISCUSSION

The study focused on the pre-formulation and development of a fixed-dose combination tablet containing sitagliptin phosphate and metformin HCl. Key physicochemical properties, including melting points (216°C for sitagliptin, 218°C for metformin), lambda maxima (267 nm and 231 nm, respectively), and FTIR spectra, confirmed the identity and purity of the drugs. Powder flow properties, assessed via angle of repose (30–38°) and Hausner's ratio (1.12–1.18), indicated good flowability, while Carr's index (10.5–13.5%) demonstrated excellent compressibility (Polyakova et al., 2022; Shantikumar et al., 2014).

The developed formulations were subjected to physicochemical characterization including weight variation, hardness thickness, and friability tests as specified in the United States Pharmacopiea (Pharmacopeia, 2016). All formulations depicted acceptable results within the limits defined in the general chapters of United States Pharmacopoeia.

The dissolution study of tablets was performed over a 12 h period using USP type II (paddle) dissolution testing apparatus. It is evident from these finding that the formulations fulfilled the criterion for sitagliptin for immediate release dosage form as more than 85% of the drug was released in the specified time period (Charoo et al., 2022). Moreover, there was no significant difference in drug release patterns from core tablet and coated tablet.

It is evident from these findings that metformin release was the highest from F2. The possible reason might be the low quantity of the release sustaining polymer in F2 (Maringanti & Nalagonda, 2013).

Bilayer and tri-layer tablets were formulated to address compatibility issues and reduce dosing frequency. Core and coated tablets exhibited acceptable weight variation, hardness (9.8–13.6 kg/cm²), friability (<0.23%), and drug assay (~100%). Dissolution studies revealed immediate release of sitagliptin (>85% within 12 h) and sustained release of metformin, with F1, F5, and F6 showing pharmaceutical equivalence to the reference product (Janumet XR) based on similarity factors ($f2 > 50$). Metformin release kinetics followed zero-order (F1, F5, F6) or first-order (F2) models, with Korsmeyer-Peppas analysis indicating non-Fickian diffusion (Costa & Sousa Lobo, 2003).

Stability studies under ICH Zone IV-A conditions (40°C/75% RH and 30°C/65% RH) confirmed no significant changes in assay or physical properties over time (González-González et al., 2022; Zothanpuii et al., 2020). The developed formulations offer a cost-effective, stable alternative to existing therapies, with potential to improve patient compliance.

## CONCLUSION

Six multilayer tablet formulations (four bilayer and two trilayer) combining immediate-release sitagliptin and sustained-release metformin were successfully developed and evaluated. Pre-formulation parameters confirmed acceptable flow and compressibility characteristics. All formulations met pharmacopeial standards for physical properties and drug content, with coating exerting no significant effect on performance.

Sitagliptin exhibited rapid release (>85% in 30 min) in all cases, meeting immediate-release criteria. Among metformin SR formulations, F2 showed the highest initial release, while F1, F5, and F6 demonstrated more consistent extended-release profiles over 10 hours. Trilayer formulations (F5 and F6) closely matched the reference product (Janumet XR) in terms of cumulative release.

Based on similarity factors ($f1$ and $f2$), formulations F1, F5, and F6 were found pharmaceutically equivalent to the innovator product for both drugs. Drug release kinetics revealed zero-order and Higuchi model fit for F1, F5, and F6, indicating controlled diffusion-based release, while F2 followed first-order kinetics.

All selected formulations remained stable under ICH-recommended conditions, confirming their robustness and shelf-life potential. Overall, the study supports F1, F5, and F6 as promising cost-effective FDC alternatives to existing commercial products.

### Recommendations

- The three pharmaceutically equivalent formulations may be subjected to in-vivo studies to select the best formulation.
- The optimized formulation may be manufactured at commercial scale and marketed to meet the local needs as well as exported to generate foreign revenue.

## REFERENCES


1. Charoo, N. A., Abdallah, D. B., Bakheit, A. A., Haque, K. U., Hassan, H. A., Abrahamsson, B., Cristofoletti, R., Langguth, P., Mehta, M., & Parr, A. (2022). Biowaiver monograph for immediate-release solid oral dosage forms: sitagliptin phosphate monohydrate. *Journal of pharmaceutical sciences*, *111*(1), 2-13.
2. Costa, P., & Sousa Lobo, J. (2003). Evaluation of mathematical models describing drug release from estradiol transdermal systems. *Drug development and industrial pharmacy*, *29*(1), 89-97.
3. González-González, O., Ramirez, I. O., Ramirez, B. I., O'Connell, P., Ballesteros, M. P., Torrado, J. J., & Serrano, D. R. (2022). Drug stability: ICH versus accelerated predictive stability studies. *Pharmaceutics*, *14*(11), 2324.
4. Jha, P. K., Shukla, H., Makwana, A., & Kakkad, A. (2023). Pharmacotherapy of type 2 diabetes mellitus. In *Type 2 Diabetes in 2024-From Early Suspicion to Effective Management*. IntechOpen.
5. Kant, P., Saini, R., & Patil, S. (2024). A REVIEW ON PROCESS VALIDATION OF EXTENDED RELEASE BI-LAYERED TABLET CONTAINING DAPAGLIFLOZIN, SITAGLIPTIN & METFORMIN HYDROCHLORIDE.
6. Kelleher, J. F., Madi, A. M., Gilvary, G. C., Tian, Y., Li, S., Almajaan, A., Loys, Z. S., Jones, D. S., Andrews, G. P., & Healy, A. M. (2019). Metformin hydrochloride and sitagliptin phosphate fixed-dose combination product prepared using melt granulation continuous processing technology. *Aaps PharmSciTech*, *21*(1), 23.
7. Maringanti, P. S., & Nalagonda, C. (2013). Formulation and evaluation of sitagliptin phosphate and metformin hydrochloride trilayered tablets. *International Journal of Drug Delivery*, *5*(1), 15.
8. Petersen, M. C., & Shulman, G. I. (2018). Mechanisms of insulin action and insulin resistance. *Physiological reviews*.
9. Pharmacopeia, U. (2016). USP 39-NF34. the USP Convention. Rockville,

10. Polyakova, E., Sabirzyanov, D., Prozorova, N., & Foteeva, A. (2022). Physicochemical properties and methods for the determination of metformin hydrochloride (A Review). *Pharmaceutical Chemistry Journal*, *55*(10), 1119-1125.
11. Sarkar, B. K., Akter, R., Das, J., Das, A., Modak, P., Halder, S., Sarkar, A. P., & Kundu, S. (2019). Diabetes mellitus: A comprehensive review. *Journal of Pharmacognosy and Phytochemistry*, *8*(6), 2362-2371.
12. Shantikumar, S., Sreekanth, G., SurendraNath, K., JaferValli, S., & Satheeshkumar, N. (2014). Compatibility study between sitagliptin and pharmaceutical excipients used in solid dosage forms. *Journal of Thermal Analysis and Calorimetry*, *115*(3), 2423-2428.
13. Tripathi, B. K., & Srivastava, A. K. (2006). Diabetes mellitus: complications and therapeutics. *Med Sci Monit*, *12*(7), 130-147.
14. Zothanpuii, F., Rajesh, R., & Selvakumar, K. (2020). A review on stability testing guidelines of pharmaceutical products. *Asian J. Pharm. Clin. Res*, *13*(10), 3-9.