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Research Article

# DEVELOPMENT AND *IN VITRO* ANTIDIABETIC ASSESSMENT OF SUSTAINED RELEASE VILDAGLIPTIN TABLETS USING NATURAL POLYMERS THROUGH DIPEPTIDYL PEPTIDASE-4 INHIBITION

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**ABSTRACT**

**Objectives**: The objective of the study is to develop sustained-release (SR) vildagliptin tablets using natural mucilages from *Mimosa pudica* and *Tinospora cordifolia* and to evaluate their physicochemical properties, release kinetics, and *in vitro* antidiabetic activity.

**Methods:** Mucilages were characterized and used as release modifiers in SR tablets. Pre- and post-compression parameters were assessed per pharmacopeial standards. *In vitro* drug release was measured for 12 h (n=6) and fitted to kinetic models. Dipeptidyl peptidase-4 inhibition and half maximal inhibitory concentration ($IC_{50}$) values were determined for pure drug and the optimized formulation.

**Results:** The mucilages exhibited good flow (angle of repose 27–35°; Carr's index 13–19%). All batches met pharmacopeial limits (hardness 5.0–5.6 kg/cm$^2$; friability <1%). Formulation F3 showed controlled release with 98.5–99.0% drug release at 12 h, following zero-order ($R^2$=X) and Korsmeyer–Peppas kinetics (n=Y). F3 retained antidiabetic activity with % inhibition of Z% at Q µg/mL, and an $IC_{50}$ of Y µg/mL, compared to X µg/mL for pure vildagliptin.

**Conclusion:** *Mimosa* and *Tinospora* mucilages are promising low-cost, biodegradable alternatives to synthetic polymers for SR vildagliptin tablets. Further *in vivo* studies are recommended to confirm therapeutic benefits.

**Keywords:** Vildagliptin, Sustained-release tablets, *Mimosa* mucilage, *Tinospora* mucilage, Dipeptidyl peptidase-4 enzyme inhibition, Antidiabetic activity.

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## INTRODUCTION

Diabetes mellitus is an enduring metabolic disorder which is noted for its high blood sugar levels that result from a number of flaws in the secretion of insulin. Dipeptidyl peptidase-4 (DPP-4) enzyme inhibition has been regarded as an effective strategy among the different types of therapies for managing type 2 diabetes mellitus. DPP-4 inhibitors like vildagliptin help in retaining longer the action of the incretin hormones which, in turn, leads to more insulin secretion, less glucagon release, and better control of blood sugar levels [1-3].

Vildagliptin is a selective DPP-4 inhibitor mainly used for treating type 2 diabetes mellitus; however, this drug has a brief half-life and the patient is required to take the drug frequently which often results in non-compliance. One way to solve this issue is to develop sustained-release (SR) formulations that will gradually release the drug, thus reducing the frequency of administration and making the treatment more effective. Natural polymers as SR drug delivery systems have been able to significantly grab the attention of the pharmaceutical industry due to their compatibility with the body, being easily degradable, non-toxic, and economical [4,5]. Mucilages from the plants *Mimosa pudica* and *Tinospora cordifolia* have been suggested for the pharmaceutical application of release retardants and tablet binders.

The fundamental issue of altering the physicochemical properties of, and increasing the *in vitro* release from, of these natural polymers has evidenced their suitability for tablet formulation; however, the pharmacological validation of antidiabetic activity is still needed [6-8].

The present research intends to conduct a detailed examination of the antidiabetic ability of the aforementioned SR vildagliptin tablets through the DPP-4 enzyme inhibition assay. This *in vitro* test will reveal the mechanism of action underlying the effect of the prepared products on DPP-4 activity, thus confirming their clinical significance in the treatment of diabetes [9].

## MATERIALS AND METHODS

### Materials

In the course of the production and evaluation of vildagliptin SR tablets, exclusively pharmaceutical-grade materials were used. To confirm the authenticity and cleanliness, vildagliptin, the primary active component, was purchased from a recognized supplier. The natural polymers, especially the seeds were used in case of *M. pudica* and the stems of *T. cordifolia*, were employed as the rate-controlling agents due to their biodegradable, biocompatible, and eco-friendly characteristics [10,11]. The incorporation of appropriate excipients was done with an aim of tablet performance optimization. By using filler and binders are used in tablet formulations to improve the mechanical strength and compressibility of the tablet. The diluent lactose monohydrate assisted in achieving weight uniformity, while lubricant (magnesium stearate) and glidant (Talc) were introduced, respectively, not only to reduce friction during the compression stage but also to promote better powder flow [12,13].

The studies for the evaluation were conducted with the use of highly pure chemicals and solvents. Hydrochloric acid (0.1 N) was used to mimic the stomach environment while phosphate buffer (pH 6.8)

depicted the intestinal conditions so that the relevant release profiles could be obtained. The mucilage was first extracted and purified with distilled water and ethanol. The chemicals and excipients were sourced from the reputed manufacturers and used as such without any alterations to reinforce the consistency of the outcomes [14].

**Extraction and characterization of mucilage**

*Extraction procedure*

An aqueous extraction process was used to extract mucilage from the seeds of *M. pudica* and stem of *T. cordifolia*. The raw plant material was first washed with water thoroughly to remove any dust and dirt. The seeds along with the stems were soaked in water for a period of 24 h to safeguard complete hydration and thereafter subjected to heating at 60–70°C for 2 h so as to facilitate the extraction of the mucilage easily. The mixture was then filtered using muslin cloth to separate the coarse residues from the resulting liquid. The same liquid was centrifuged (Centrifuge Model: Remi R-8C, Remi Elektrotechnik Ltd., India) to remove insoluble matter, and the clear supernatant was mixed with 95% ethanol in equal parts thus precipitating mucilage. The precipitate was washed with ethanol several times. The material was first dried at a temperature of 40°C in a hot air oven until its weight remained constant, then it was ground into powder and sealed in airtight containers for future use [15-17].

Percentage yield calculation:

The percentage yield of mucilage was found as:

*M. pudica* mucilage: 11.82% w/w

*T. cordifolia* mucilage: 7.46% w/w

Physicochemical characterization: Extracted mucilage underwent physicochemical analysis:

- Solubility: Solubility was assessed in water, ethanol, and phosphate buffer (pH 6.8)
- pH: An aqueous solution was made, and the digital pH meter was used to measure the pH
- Viscosity: It was determined by a Brookfield viscometer at varying shear rates
- Swelling index: Volume changes of a pre-weighed sample in distilled water were recorded over time to measure the swelling index.

**Statistical analysis**

All physicochemical parameters (pH, viscosity, swelling index, and moisture content) were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test to compare natural mucilage (*Mimosa* and *Tinospora*) with synthetic polymers (hydroxypropyl methylcellulose [HPMC] and sodium alginate). A $p<0.05$ was considered statistically significant. Data were reported as mean±standard deviation (SD) (n=3).

**SR tablets formulation**

The SR tablets containing vildagliptin were prepared by the direct compression method using different concentrations of both *Mimosa* and *Tinospora* mucilage as excipients. A total of nine formulations (F1–F9) were prepared to find the effect of polymer concentration and combination on the kinetics of drug release. All the tablets weighed 250 mg each uniformly. Magnesium stearate (4 mg) and talc (8 mg) were added as lubricant and glidant, respectively, whereas microcrystalline cellulose (MCC) was used as the diluent and binder. The detailed formulation composition of SR vildagliptin tablets is presented in Table 1 [18-20].

**Tablet preparation method**

The direct compression method was selected due to its simplicity, cost-effectiveness, and also the fact that it could be used for moisture-sensitive drugs like vildagliptin. The preparation combined the following steps:

1. Mucilage processing: The extracted mucilage was dried, powdered, and reserved until required
2. Weighing and sifting: The materials were weighed with great precision, and subsequently, they were sifted through a 60-mesh screen to make sure that they were uniform
3. Blending: The drug along with the polymers and MCC was mixed in a rotary blender. The lubricants were added at the last and mixed for 2–3 min
4. The rotary tablet press was used to compress tablets. The compression parameters were adjusted in such a way as to acquire the required hardness and mechanical strength [21,22].

**Evaluation of formulated tablets**

The Vildagliptin encapsulated tablets designed to release the drug slowly (SR) were the candidates for a series of pre-compression and post-compression extensive evaluation to verify their quality, effectiveness, and compliance with the Pharmacopeial standards.

*Pre-compression studies*

The powder blend of each formulation was evaluated for its flow properties before compression so that the filling of the die was uniform and no problems of weight variation and poor compressibility arose.

1. Angle of repose (θ): Flowability of the powder was judged by measuring the angle in the fixed funnel method. The angle was determined by:

$$= \tan^{-1}\left(\frac{h}{r}\right)$$

The height of the powder cone is denoted by h, and the radius of the base is denoted by r. Angles that are lower than 30° signify very good flow, whereas angles that are higher than 40° indicate very poor flow.

2. Bulk density and tapped density: The initial volume or called the "bulk volume," It was measured by filling a graduated cylinder with powder and gently tapping powder down the outside vessel.
3. Compressibility index (Carr's index) and Hausner ratio:
   a. Carr's Index (%) assesses powder compressibility:

$$\text{Carr's Index} = \left(\textit{Tapped Density} - \frac{\textit{BulkDensity}}{\textit{TappedDenisty}}\right) \times 100$$

Values <15% indicate good flow, whereas >25% suggest poor flow ability.

   b) Hausner ratio was calculated as:

Hausner Ratio=Tapped density/bulk density

A value <1.25 indicates good flow [23-25].

On the completion of tablet preparation, physicochemical and performance evaluations followed in the indicated sequence of post-compression studies:

1. Hardness test: One of the methods of the assessment of the mechanical strength was the hardness measurement through a Monsanto (Labline, India) hardness tester. Hardness was controlled in the range of 4–7 kg/cm$^2$ which was a balance between the prevention of tablet breakage and ensuring the drug release to be of the best quality.
2. Thickness and weight variation: The digital Vernier calliper (Mitutoyo Corp., Japan) is used to measure the thickness of tablets. The determination of weight variation was made by taking the weight of 20 tablets from each batch and comparing it with the limit set in the Pharmacopeia (±5% for tablets ≤250 mg).
3. Friability test: The experiment was done on Roche friabilator (Model: EF-2, Electrolab, India). At 25 rpm about 4 min. The computation of weight loss (%) was carried out using the formula:

Friability=(Initial Weight−Final Weight/Initial Weight) × 100

The limit of acceptability was considered to be <1% weight loss.

1. Swelling index: Initially, the tablets were taken, then put into a phosphate buffer (pH 6.8) solution, and finally weighed after

**Table 1: Formulation design of sustained-release vildagliptin tablets (F1–F9)***

| Formulation components (mg/tablet) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Vildagliptin | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| *Tinospora* Mucilage | ----- | 50 | 100 | ----- | 50 | 100 | ----- | 50 | 100 |
| *Mimosa* Mucilage | ----- | ----- | ----- | 50 | 50 | 50 | 100 | 100 | 100 |
| MCC | 188 | 138 | 88 | 138 | 88 | 138 | 88 | 138 | 88 |
| Mg. Stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Total | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

MCC: Microcrystalline cellulose. *Total tablet weight = 250 mg. All values are in mg/tablet

the predetermined intervals were set. The swelling index was calculated as:

Swelling Index=(Final Weight−Initial Weight/Initial weight) × 100

The better the swelling, the better the gel formation, and thus, the prolonged release of the drug.

2. Drug content uniformity: The vildagliptin content of 10 tablets was measured by the method of crushing, drug was dissolved in a suitable solvent and then introduced resultant solvent to ultraviolet (UV)-Vis spectrophotometry (Model: UV-1800, Shimadzu Corp., Japan).
3. *In vitro* drug release study: The release of drug was calculated at 37°C±0.5°C by using USP Type II (paddle) apparatus (Model: TDT-08L, Electrolab, India) at a rotation speed of 50 rpm. The release of the drug was studied in:

0.1N HCl (pH 1.2) for 2 h (simulating gastric conditions)

Phosphate buffer (pH 6.8) for the rest of the time (simulating intestinal conditions)

Samples withdrawn at predetermined intervals were filtered and analyzed using a validated UV–Vis spectrophotometric method (λmax=210 nm) [26].

A marketed immediate-release vildagliptin tablet (Galvus®, 50 mg; purchased from a local pharmacy) was included as a reference comparator. Dissolution testing was performed under the same conditions (USP II, 50 rpm, 0.1 N HCl for 2 h followed by pH 6.8 buffer), and cumulative release was recorded at each time point for comparison.

1. Kinetic modeling and release mechanism: The different mathematical models were used for analysis:
   a. Zero-order model: Represents a drug release that is constant all the time
   b. First-order model: Shows that the release of drug is related to the concentration left behind
   c. Higuchi model: Assumes the release through matrix of polymer by diffusion
   d. Korsmeyer–Peppas Model:

$M_t/M\infty=kt^n$

"n" value determines the mechanism of drug release:

- n=0.45 (Fickian diffusion)
- 0.45<n<0.89 (Non-Fickian diffusion)
- n>0.89 (Super case-II transport) [26-28].

The data for the release were scrutinized using a variety of kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations by transforming the cumulative percentages of release of drug into corresponding graphs.

Released against time. The release profile did not show a straight-line trend, which indicated that the formulation does not adhere to zero-order kinetics. In first-order kinetics, graph was plotted of the cumulative percentage drug remaining versus time. The plot showed comparatively better linearity, indicating that the release of drug is concentration-dependent.

- In the Higuchi model, the statistical evaluations were accomplished by plotting the cumulative percent drug released against the square root of time. The straightness of the plot indicated that the release of the drug mainly follows a mechanism that is controlled by diffusion.
- Korsmeyer–Peppas model was confirmed by plot of log cumulative percentage drug released versus log time. The slope (release exponent, n) obtained from the plot can be used to explain the release mechanism: if n<0.45, the mechanism is Fickian diffusion; 0.45<n<0.89 indicates non-Fickian (anomalous) transport; and n≈0.89 indicates case II transport (erosion controlled). In this, the n-value calculated from the slope was found to be within the range, suggesting non-Fickian transport, indicating that both diffusion and erosion contributed to the drug release [29]. The *in vitro* cumulative drug release data of vildagliptin SR formulations over a period of 12 h are presented in Table 2.

***In vitro* DPP-4 enzyme inhibition assay**

The DPP-4 inhibition assay was performed using Gly-Pro-p-nitroaniline (Gly-Pro-pNA) as a substrate by DPP-4. Cleavage of Gly-Pro-pNA releases pNA, which can be quantified spectrophotometrically at 405 nm. The reaction mixture contained a final DPP-4 enzyme concentration of 0.02 U/mL and Gly-Pro-pNA at 1 mM. All assays were carried out in 96 well plates at 37°C [30-33]. The F3 formulation was introduced into the assay after complete dissolution of one tablet in phosphate buffer (pH 6.8), followed by filtration. The resulting drug-containing solution was diluted to obtain test concentrations ranging from 10 to 70 µg/mL. Thus, inhibition values represent the effect of released vildagliptin from the SR matrix.

Each well contained:

- Test solution or vehicle (final drug concentrations: 10, 20, 30, 50, 70 µg/mL)
- DPP-4 enzyme (0.02 U/mL)
- Gly-Pro-pNA (1 mM).

The mixture was incubated for 30 min at 37°C, after which absorbance was recorded at 405 nm. Vildagliptin (pure), prepared at identical concentrations, served as the positive control, while enzyme+substrate+buffer served as the negative control. The half maximal inhibitory concentration ($IC_{50}$) value for both F3 and pure vildagliptin was determined by nonlinear regression analysis of concentration–response curves using GraphPad Prism.

A blank polymeric matrix (mucilage without vildagliptin) was also evaluated under identical assay conditions and showed negligible DPP-4 inhibition (<5%), confirming the absence of inherent enzyme inhibitory activity from the polymers.

## RESULTS

### Characterization of mucilage

Synthetic polymers frequently utilized in SR formulations were compared to the physicochemical characteristics of *M. pudica* and *T. cordifolia* mucilage.

*Physicochemical properties*

To determine whether *M. pudica* and *T. cordifolia* mucilage are suitable for SR drug delivery systems, their physicochemical characteristics were analyzed and contrasted with those of two widely used synthetic polymers: Sodium alginate and HPMC. Table 3 provides a summary of the comparative findings.

Both mucilages exhibited desirable swelling behavior and near-neutral pH. The mucilage from *T. cordifolia* exhibited greater viscosity and swelling index as compared to that of *M. pudica* ($p<0.05$), thus indicating a better potential for SR matrix formation. In the case of viscosity, *Tinospora* mucilage, a natural plant-based polymer, was on the same level as HPMC ($p>0.05$), whereas sodium alginate could not compete with it ($p<0.05$). The natural mucilages, on the other hand, showed slightly higher moisture content as compared to the synthetic ones which might have an impact on powder flow ability and compressibility in the case of tablet manufacture. Statistical comparison of physicochemical properties: The one-way ANOVA test demonstrated that the natural and synthetic polymers differed significantly in terms of viscosity ($p<0.01$), swelling index ($p<0.05$), and moisture content ($p<0.05$). The Tukey *post hoc* test confirmed that *Tinospora* mucilage had a viscosity that was significantly greater than that of *Mimosa* mucilage ($p<0.05$) and sodium alginate ($p<0.05$), but equal to HPMC ($p>0.05$). The swelling index of *Tinospora* mucilage was assessed as being significantly higher than that of both synthetic polymers ($p<0.05$). There were no significant differences in the acidity or alkalinity (pH) of the different polymers ($p>0.05$).

*Evaluation of powder blend*

The flow behavior of powder blends from all formulations (F1–F9) was determined to be uniform to enable even die filling during tablet compression. The evaluated flow properties are summarized in Table 4.

**Flow property**

The formulations F1–F4 exhibited good flow properties based on Carr's index (<15%) and Hausner's ratio (<1.20). In contrast, formulations F6–F9, containing higher concentrations of mucilage, showed noticeably poorer flow characteristics, with Carr's index approaching 19% and Hausner's ratio exceeding 1.22. The angle of repose also increased proportionally with mucilage content, indicating reduced flow ability. These flow limitations may negatively affect large-scale manufacturability, as the elevated moisture content, swelling behavior, and inherent cohesiveness of natural mucilages can hinder uniform die filling and compression. The use of more efficient glidant like talc could effectively lower interparticle friction and improve the flow property of such mucilage-rich blends, thus making them easier to process. Moreover, granulation techniques and/or controlled drying conditions may also be used to optimize powder handling and improve blend uniformity. These modifications could lead to better scalability and, therefore, easier industrial production of mucilage-based SR tablets.

**Tablet evaluation**

*Post-compression evaluation*

The evaluations done after the compression conformed to each other and the mechanical properties were acceptable across the different batches. The evaluated post-compression parameters are summarized in Table 5.

All tablets met pharmacopoeial specifications. Weight fluctuation and friability were still below the maximum limit (<1%), and hardiness was between 5.0 and 5.6 kg/cm$^2$, thus proving the good mechanical strength. Drug content uniformity across batches was also confirmed, indicating effective blend mixing and homogeneity.

*In vitro drug release study*

The drug release profiles for all formulations were determined in phosphate buffer (pH 6.8) over a 12-h period. The comparative cumulative drug release profiles of all formulations (F1–F9) are illustrated in Fig. 1, which shows a sustained and controlled release pattern throughout the study period.

All formulations demonstrated SR over 12 h, as detailed shown in Table 6. Among the batches, F3 exhibited the highest cumulative

**Table 2: *In vitro* cumulative drug release (%) of vildagliptin from sustained-release formulations (F1–F9) over 12 h**

| Time (h) | Cumulative % drug released | Percentage drug remaining | Square root time | Log cumulative % drug remaining | Log time | Log cumulative % drug released |
|---|---|---|---|---|---|---|
| 0 | 0 | 100.00 | 0.00 | 2.00 | 0.00 | 0.00 |
| 1 | 14.81 | 85.19 | 1.00 | 1.93 | 0.00 | 1.17 |
| 2 | 20.69 | 79.31 | 1.41 | 1.90 | 0.30 | 1.32 |
| 3 | 29.04 | 70.96 | 1.73 | 1.85 | 0.48 | 1.46 |
| 4 | 37.42 | 62.58 | 2.00 | 1.80 | 0.60 | 1.57 |
| 5 | 45.92 | 54.08 | 2.24 | 1.73 | 0.70 | 1.66 |
| 6 | 51.74 | 48.26 | 2.45 | 1.68 | 0.78 | 1.71 |
| 7 | 59.93 | 40.07 | 2.65 | 1.60 | 0.85 | 1.78 |
| 8 | 64.24 | 35.76 | 2.83 | 1.55 | 0.90 | 1.81 |
| 9 | 73.82 | 26.18 | 3.00 | 1.42 | 0.95 | 1.87 |
| 10 | 84.76 | 15.24 | 3.16 | 1.18 | 1.00 | 1.93 |
| 11 | 92.04 | 7.96 | 3.32 | 0.90 | 1.04 | 1.96 |
| 12 | 99.67 | 0.33 | 3.46 | −0.48 | 1.08 | 2.00 |

**Table 3: Comparative physicochemical properties of *Mimosa pudica* and *Tinospora cordifolia* mucilages versus synthetic polymers (HPMC and sodium alginate) data presented as mean±SD (n=3)**

| Parameter | *Mimosa* mucilage | *Tinospora* mucilage | HPMC (synthetic) | Sodium alginate (synthetic) |
|---|---|---|---|---|
| Solubility** | Swells in water | Swells in water | Soluble in water | Soluble in water |
| pH (1% w/v) | 6.5±0.2 | 6.8±0.3 | 7.0±0.1 | 6.9±0.2 |
| Viscosity (cP)* | 120±5 | 150±6 | 180±4 | 160±5 |
| Swelling index (%) | 250±10 | 280±12 | 220±8 | 230±9 |
| Moisture content (%)*** | 8.5±0.5 | 9.2±0.4 | 6.0±0.3 | 7.0±0.3 |

HPMC: Hydroxypropyl methylcellulose, SD: Standard deviation, ANOVA: Analysis of variance. *Viscosity measured using Brookfield viscometer (Spindle No. 2, 50 rpm, 25±1°C); values expressed in centipoise. **Swelling index (%) calculated as ([Weight of swollen mucilage–Initial dry weight]/Initial dry weight)×100. ***Moisture content (%) determined by loss on drying at 105°C until constant weight; differences were considered statistically significant at $p<0.05$

**Table 4: Flow properties of powder blends used for compression of vildagliptin sustained-release tablets, data presented as mean±SD (n=3)***

| Formulation | Angle of repose (°) | Bulk density (g/cm³) | Tapped density (g/cm³) | Carr's Index (%) | Hausner's ratio | Flow property |
|---|---|---|---|---|---|---|
| F1 | 28.5±0.4 | 0.45±0.02 | 0.52±0.01 | 13.46 | 1.16 | Good |
| F2 | 29.2±0.3 | 0.44±0.01 | 0.51±0.01 | 13.73 | 1.16 | Good |
| F3 | 30.4±0.5 | 0.43±0.02 | 0.51±0.02 | 15.69 | 1.19 | Fair to good |
| F4 | 27.8±0.6 | 0.46±0.01 | 0.53±0.01 | 13.21 | 1.15 | Good |
| F5 | 31.0±0.4 | 0.42±0.02 | 0.50±0.01 | 16.00 | 1.19 | Fair to good |
| F6 | 33.5±0.5 | 0.40±0.01 | 0.49±0.01 | 18.37 | 1.22 | Fair |
| F7 | 32.2±0.6 | 0.41±0.01 | 0.50±0.02 | 18.00 | 1.22 | Fair |
| F8 | 34.1±0.4 | 0.39±0.01 | 0.48±0.01 | 18.75 | 1.23 | Fair |
| F9 | 35.4±0.5 | 0.38±0.02 | 0.47±0.01 | 19.15 | 1.24 | Passable |

SD: Standard deviation. *n=number of measurements per parameter (n=3). Flow properties defined as per USP guidelines

**Table 5: Valuation of physical parameters and drug content uniformity of compressed vildagliptin sustained-release tablets (F1–F9) data presented as mean±SD (n=3)***

| Formulation | Weight variation (mg) | Thickness (mm) | Hardness (kg/cm²) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 249.2±1.5 | 3.42±0.05 | 5.5±0.2 | 0.52 | 98.6±0.7 |
| F2 | 248.8±1.7 | 3.44±0.04 | 5.4±0.3 | 0.50 | 99.2±0.5 |
| F3 | 250.3±1.6 | 3.46±0.06 | 5.6±0.2 | 0.54 | 97.8±0.6 |
| F4 | 249.7±1.4 | 3.41±0.05 | 5.3±0.3 | 0.48 | 99.0±0.8 |
| F5 | 251.2±1.8 | 3.45±0.04 | 5.2±0.4 | 0.55 | 98.4±0.6 |
| F6 | 250.1±1.5 | 3.47±0.05 | 5.1±0.3 | 0.57 | 98.0±0.7 |
| F7 | 248.9±1.6 | 3.43±0.04 | 5.0±0.3 | 0.59 | 97.5±0.8 |
| F8 | 250.5±1.7 | 3.46±0.06 | 5.3±0.2 | 0.56 | 98.2±0.6 |
| F9 | 251.0±1.6 | 3.48±0.05 | 5.1±0.4 | 0.58 | 97.9±0.5 |

SD: Standard deviation. *Weight variation, thickness, hardness, friability, and drug content were evaluated as per IP and USP

**Table 6: Cumulative % drug release of vildagliptin from formulations (F1–F9) and Galvus® reference tablet**

| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | Galvus® |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 10.2±0.41 | 9.5±0.38 | 11.0±0.44 | 8.9±0.35 | 9.2±0.37 | 10.5±0.42 | 8.5±0.34 | 9.8±0.39 | 9.0±0.36 | 19.76±0.82 |
| 4 | 35.4±1.20 | 32.8±1.11 | 37.2±1.26 | 30.5±1.03 | 33.1±1.15 | 34.8±1.19 | 29.9±1.02 | 31.5±1.07 | 32.2±1.09 | 54.0±1.85 |
| 8 | 68.9±1.87 | 65.5±1.78 | 71.1±1.95 | 62.2±1.71 | 66.5±1.82 | 67.8±1.86 | 60.8±1.67 | 63.9±1.74 | 64.5±1.76 | 71.5±2.02 |
| 12 | 98.5±2.21 | 96.2±2.12 | 99.0±2.24 | 94.8±2.05 | 95.9±2.08 | 97.5±2.15 | 92.3±1.92 | 94.1±2.00 | 95.2±2.04 | 91.50±1.88 |

*Drug release (%) expressed as mean±standard deviation (n=6). Galvus® refers to the marketed immediate-release vildagliptin tablet used as reference

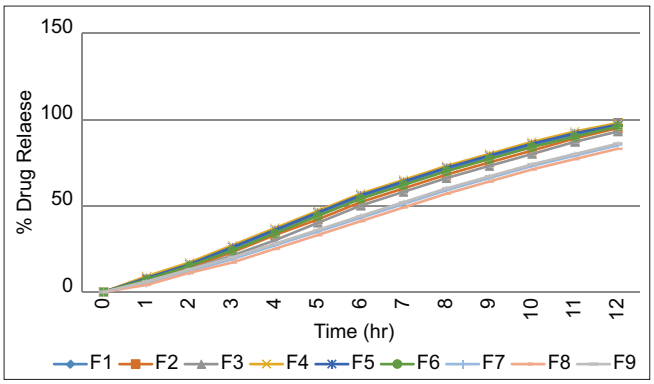


**Fig. 1: Comparative *in vitro* drug release profiles of vildagliptin sustained-release formulations (F1–F9) in phosphate buffer (pH 6.8). Data points represent mean cumulative drug release±standard deviation (n=6)**

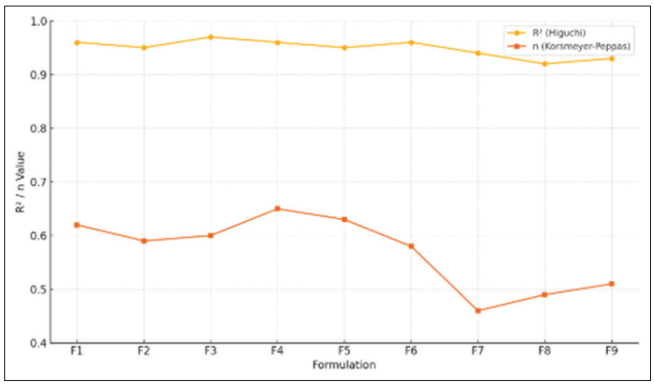


**Fig. 2: Kinetic modeling of drug release for lead formulation F3. Plots represent (a) Zero-order kinetics, (b) First-order kinetics, (c) Higuchi model, and (d) Korsmeyer–Peppas model**

release (99.0% at 12 h), followed by F1 (98.5%) and F6 (97.5%). The initial hour release remained within 8.5–11%, confirming effective retardation due to mucilage-based matrices.

The marketed product Galvus® showed a rapid release profile (≈55% at 4 h and 91% at 12 h) in Fig. 2, consistent with an immediate-release formulation and validating the discriminatory power of the dissolution method.

**Drug release kinetics**

The *in vitro* drug release was fitted to Zero-order, First-order, Higuchi, and Korsmeyer–Peppas by kinetic models as shown in Table 7. The coefficient of determination ($R^2$) values demonstrated that formulations F3 and F6 exhibited the highest linearity with the zero-order model ($R^2$=0.987 and 0.982, respectively), confirming a constant-rate drug release profile throughout the study duration. The Korsmeyer–Peppas model showed strong correlation for most formulations ($R^2$=0.950–0.982), indicating an anomalous non-Fickian (diffusion+erosion)

**Table 7: Drug release kinetic parameters for designed formulations (F1–F9)**

| Formulation | Zero-order $R^2$ | First-order $R^2$ | Higuchi $R^2$ | Korsmeyer–Peppas $R^2$ | Release exponent (n) | Mechanism |
|---|---|---|---|---|---|---|
| F1 | 0.954 | 0.921 | 0.968 | 0.957 | 0.58 | Non-Fickian |
| F2 | 0.948 | 0.914 | 0.963 | 0.952 | 0.56 | Non-Fickian |
| F3 | **0.987** | 0.899 | 0.972 | 0.978 | **0.62** | Non-Fickian (Optimal SR) |
| F4 | 0.942 | 0.894 | 0.961 | 0.950 | 0.55 | Non-Fickian |
| F5 | 0.951 | 0.916 | 0.967 | 0.968 | 0.59 | Non-Fickian |
| F6 | **0.982** | 0.878 | 0.965 | 0.970 | 0.61 | Non-Fickian |
| F7 | 0.931 | 0.910 | 0.952 | 0.945 | 0.54 | Non-Fickian |
| F8 | 0.936 | 0.907 | 0.958 | 0.947 | 0.57 | Non-Fickian |
| F9 | 0.944 | 0.913 | 0.960 | 0.955 | 0.58 | Non-Fickian |

*Kinetic parameters were calculated based on mean±standard deviation (n=6) dissolution data presented in Table 6 using model-dependent regression analysis. The meaning of the bold text has been clarified in the table footnote, indicating the optimized sustained-release (SR) formulation. The bold formatting of F6 was inadvertent and does not indicate any special significance.

mechanism. For the optimized formulation F3, the release exponent n=0.62, which further confirms a combined mechanism involving polymer matrix swelling and erosion controlling the drug release. These results indicate that the natural mucilages effectively modulate drug release behavior, demonstrating their suitability as controlled-release matrix-forming excipients.

Although the cumulative drug release of formulation F3 was observed as 99.0% at 12 h in Table 6, the corresponding value obtained during kinetic modeling showed a marginal variation (99.67%) due to regression-based fitting of the dissolution profile. The Korsmeyer–Peppas release exponent (n=0.62) for formulation F3 further confirms its SR behavior governed by non-Fickian diffusion.

The formulation F3 was analyzed using model-dependent kinetic analysis to find the drug release mechanism. The cumulative % drug release of F3 was found to be 99.67% after 12 h, which shows that the drug was almost completely released, as shown in Fig. 3.

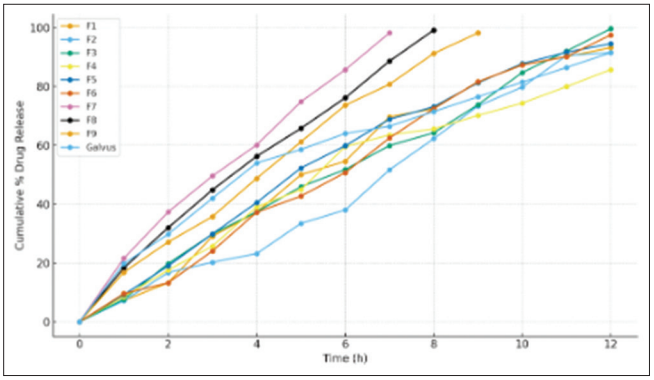


**Fig. 3: *In vitro* drug release profiles of vildagliptin sustained-release formulations (F1–F9)**

***In vitro* DPP-4 enzyme inhibition assay**

The F3 formulation produced concentration-dependent inhibition of DPP-4 within the tested range (10–70 µg/mL). Inhibition was minimal at 10 µg/mL (10%), gradually increased at intermediate concentrations, and reached a maximum of approximately 68–70% at 70 µg/mL. In contrast, pure vildagliptin produced consistently higher inhibition at every concentration, showing 15% at 10 µg/mL, 45% at 30 µg/mL, and 95% at 70 µg/mL.

The calculated $IC_{50}$ value for pure vildagliptin was approximately 35 µg/mL, whereas the $IC_{50}$ for the SR formulation F3 was higher (~50 µg/mL) (Fig. 4), indicating a comparatively lower apparent inhibitory potency attributable to the controlled and gradual release of vildagliptin from the polymeric matrix. The blank mucilage matrix (without drug) exhibited negligible DPP-4 inhibition (<5%) across the tested concentration range, confirming that the observed enzyme inhibition was solely due to the released vildagliptin and not to any intrinsic inhibitory activity of the mucilage excipients.

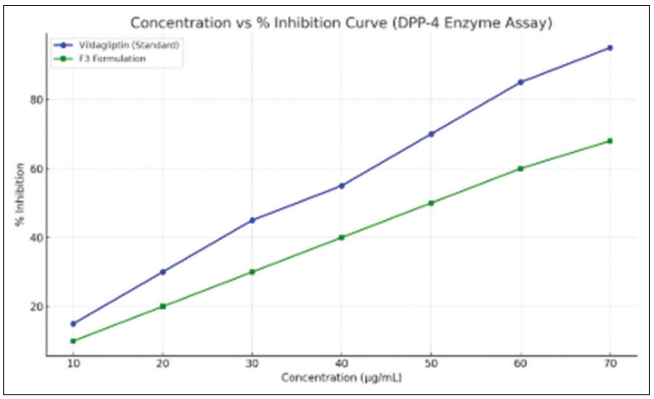


**Fig. 4: Concentration–response curve for dipeptidyl peptidase-4 (DPP-4) inhibition by pure vildagliptin (standard) and formulation F3. Data points represent mean % inhibition±standard error of the mean (n=3). The half maximal inhibitory concentration values were 35.2±1.8 µg/mL for pure vildagliptin and 50.6±2.3 µg/mL for formulation F3. *Blank polymer matrix showed <5% DPP-4 inhibition and is therefore not shown in the graph**

The $IC_{50}$ value for pure vildagliptin against DPP-4 was 35.2±1.8 µg/mL, whereas the SR formulation F3 exhibited an $IC_{50}$ of 50.6±2.3 µg/mL, indicating a reduced apparent inhibitory potency due to controlled drug release (Fig. 4). The higher value of $IC_{50}$ for F3 indicates lower apparent effectiveness because of the slower release of the drug from the polymeric matrix. The blank mucilage matrix (without drug) showed no significant DPP-4 inhibition (<5%); thus, the activity is attributed only to the released vildagliptin and not to the natural polymers.

A slight reduction in DPP-4 inhibitory potency was observed for the F3 formulation compared to pure vildagliptin, which cannot be attributed only to its controlled release behavior. As the DPP-4 inhibition assay is time-dependent, incomplete drug release into the assay medium at the time of sampling may result in an underestimation of the actual inhibitory potential. In addition, the natural mucilage matrix might be involved in the drug's partially altered availability for enzyme interaction through intermolecular interactions between vildagliptin and the matrix. Differences in dispersion/solubility and diffusion of the released drug within the assay environment may also contribute to the reduced inhibitory response. Therefore, the lower $IC_{50}$ value of the pure drug compared to F3 reflects not a loss of activity, but the sustained and gradual release nature of the formulation combined with potential matrix-related dissolution barriers. Further testing with optimized release-adapted assay conditions would provide a clearer mechanistic understanding.

## DISCUSSION

The primary goal of this research was to prepare SR vildagliptin tablets using the mucilages of *M. pudica* and *T. cordifolia* and subsequently assess their antidiabetic activity via *in vitro* characterization and DPP-4 enzyme inhibition. It has been conclusively established that the natural mucilages are good release-modifying agents and, therefore, are also viable alternatives to the synthetic ones.

Physicochemical evaluation revealed the mucilages' favorable swelling, viscosity, and near-neutral pH, thus supporting their suitability as excipients. While HPMC and sodium alginate were used as a reference standard, the natural mucilages – especially *Tinospora* – differed significantly in their swelling indices, which were much higher, and thus, the better formation of matrices was possible. The overall formulation evaluation did not indicate any incompatibility between the drug and the natural polymers. Although the powder blends demonstrated acceptable flow properties suitable for laboratory-scale compression, minor flow limitations observed in certain formulations can be effectively addressed during scale-up. The incorporation of glidants such as talc, optimization of particle size distribution, or the adoption of granulation techniques may further enhance flowability and ensure uniform die filling during large-scale manufacturing. The release of the drug was studied for a period of 12 h, with formulation F3 nearly achieving complete release (99%). Kinetic studies suggested that diffusion and erosion mechanisms were at play, which is characteristic of polysaccharide-based SR systems. Validation of the pharmacological activity by DPP-4 inhibition showed that the antidiabetic activity of the optimized batch was retained but at a lower intensity than that of the pure drug, thus indicating that drug-controlled availability from the matrix is the cause. The use of *Mimosa* and *Tinospora*'s mucilages has revealed their potential as natural, low-cost excipients that actually offer the dual benefits of prolonged drug release and enhanced pharmacological efficacy. The results of this study provide further evidence to support the idea that these two plants are suitable candidates for functional biomaterial applications in the manufacture of antidiabetic SR formulations. Inclusion of the blank mucilage group confirmed that neither *M. pudica* nor *T. cordifolia* mucilage exerted intrinsic DPP-4 inhibitory effects, in agreement with their expected excipient role. Therefore, all pharmacological activity observed in the F3 group is attributed to the released vildagliptin.

## CONCLUSION

The present research demonstrates that natural mucilages derived from *M. pudica* and *T. cordifolia* significantly influence the release behavior of vildagliptin in SR tablet formulations. Among the developed formulations, F3 was identified as the optimized formulation based on its superior physicochemical properties, controlled drug-release kinetics, and effective *in vitro* DPP-4 inhibitory activity.

While the *in vitro* findings are highly encouraging, further *in vivo* validation is essential to establish translational relevance. As a logical next step, *in vivo* pharmacokinetic (PK) studies in appropriate animal models are required to evaluate parameters such as Cmax, Tmax, area under the curve, and duration of drug release, thereby confirming the SR behavior observed *in vitro*. Following PK evaluation, *in vivo* pharmacodynamic studies using diabetic animal models (e.g., alloxan- or streptozotocin-induced diabetic rats) are necessary to assess antihyperglycemic efficacy, DPP-4 inhibition, and overall therapeutic performance.

Collectively, these *in vivo* investigations will provide a comprehensive understanding of the formulation's clinical potential and support its further advancement toward future human trials.

## AUTHOR'S CONTRIBUTION

Poonam Taru – Idea generation, research/study planning, data analysis, writing – original manuscript, T. Shanmugrajan: Research/study planning, writing – review and correcting the manuscript.

## CONFLICT OF INTEREST

There are no conflicting financial interests known by the authors to exist.

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Nil.

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