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Formulation Development and Evaluation of Chronomodulated Drug Delivery Systems for treatment of Diabetes

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ABSTRACT
The research focuses on the formulation development and evaluation of chronomodulated drug delivery systems for anti-diabetic drugs, leveraging insights from past studies to optimize the delivery of Vildagliptin microspheres. Chronomodulated drug delivery systems are designed to synchronize the release of medication with the body's natural biological rhythms, enhancing therapeutic efficacy and patient compliance. Vildagliptin microspheres were meticulously prepared using an emulsion solvent evaporation method, guided by previous findings on drug-polymer ratios, surfactant concentrations, and stirring speeds to achieve optimal particle size and drug entrapment efficiency. The microspheres exhibited controlled release properties, essential for maintaining consistent drug levels in alignment with circadian rhythms. Characterization through techniques such as scanning electron microscopy, differential scanning calorimetry, and fourier-transform infrared spectroscopy confirmed the structural integrity and compatibility of the formulated microspheres. The *in vitro* release studies demonstrated a non-Fickian, zero-order drug release pattern, highlighting the system's potential to deliver Vildagliptin effectively over a prolonged period. The results suggest that the developed Vildagliptin loaded microspheres pulsincap system hold promise for improving the management of diabetes through a chronomodulated approach, warranting further investigation through *in vivo* studies to establish clinical efficacy and safety.

Keywords: *Chronomodulated drug delivery system, Antidiabetic drug, Glycemic control, Circadian rhythm, microspheres.*

1. INTRODUCTION

The prevalence of diabetes mellitus has escalated significantly over recent decades, presenting major challenges to healthcare systems globally [1]. This chronic metabolic disorder is characterized by elevated blood glucose levels, which result from insufficient insulin production or ineffective use of insulin by the body [2]. Type 2 diabetes mellitus (T2DM) is the most common form, associated with lifestyle choices, genetic factors, and an aging population [3]. Effective diabetes management necessitates strategies that not only reduce blood glucose levels but also align with the body's physiological rhythms. Chronomodulated drug delivery systems represent a novel approach aimed at enhancing the effectiveness of antidiabetic medications while improving patient compliance [4]. By synchronizing drug release with the body's circadian rhythms, CDDS can better manage glycemic fluctuations and minimize long-term complications [5]. This research focuses on the development and assessment of a chronomodulated system utilizing Vildagliptin, a potent dipeptidyl peptidase-4 inhibitor that operates through a glucose-dependent mechanism .Vildagliptin works by inhibiting DPP-4, which increases the activity of incretin hormones that promote insulin secretion and inhibit glucagon release, thereby facilitating optimal blood glucose control [3,6]. However, conventional formulations often do not align drug release with metabolic demands, particularly during the early morning "dawn phenomenon," when blood glucose levels can spike due to increased hepatic glucose production. To overcome these limitations, this study employs an innovative formulation strategy that encapsulates Vildagliptin in polymeric microspheres integrated into a pulsatile drug delivery system [2,4]. The formulation of Vildagliptin-loaded microspheres was achieved using the emulsion solvent evaporation technique, known for producing spherical particles with high drug loading efficiency. To optimize process parameters and achieve desired physicochemical properties, a Box-Behnken Design was utilized [7]. This statistical approach allowed for a systematic examination of how independent variables—such as polymer concentration, calcium ion levels, and stirring speed—affect critical response factors like particle size, entrapment efficiency, and drug release kinetics. The optimized microspheres displayed uniform size distribution, high encapsulation efficiency, and smooth surface morphology as confirmed by scanning

electron microscopy. Compatibility assessments between Vildagliptin and the selected polymers were conducted using Fourier-transform infrared spectroscopy and differential scanning calorimetry. Fourier-transform infrared spectroscopy results indicated no significant interactions between the drug and polymer matrix, ensuring Vildagliptin's chemical stability within the formulation [4]. Differential scanning calorimetry analysis revealed a distinct endothermic peak corresponding to Vildagliptin's melting point, confirming its crystalline nature and thermal stability within the microsphere composition. A key aspect of this research is integrating the optimized microspheres into a pulsincap system—a sophisticated delivery platform designed for chronotherapeutic applications. The pulsincap system was constructed using formaldehyde-treated hard gelatin capsules filled with Vildagliptin-loaded microspheres and sealed with hydrogel plugs. This design allows for an initial lag phase followed by a burst release of the drug timed to coincide with early morning increases in blood glucose levels. In vitro dissolution testing revealed a zero-order release pattern, indicative of consistent drug release over time. The observed non-Fickian diffusion mechanism further validated the system's capability for controlled and predictable drug delivery[8]. To ensure robustness and reliability, comprehensive evaluations were conducted on the pulsincap system. These assessments included weight variation, drug content uniformity, and mechanical integrity—all meeting pharmacopeia standards. Stability tests were performed under accelerated and long-term conditions to simulate real-world storage scenarios [9]. Results indicated that the formulation maintained its physicochemical properties and drug release characteristics throughout the study period. The in vitro findings underscore the significant potential of Vildagliptin-loaded microspheres integrated into a pulsincap system for chronomodulated drug delivery [1,6]. By aligning drug release with circadian rhythms, this system addresses challenges such as suboptimal timing in medication administration and patient non-compliance. Furthermore, the controlled release profile achieved minimizes fluctuations in plasma drug concentrations, thereby reducing hypoglycaemia risks—an important consideration in diabetes management[7]. While promising *in vitro* results have been obtained, further research is necessary to assess in vivo performance of the developed system. Preclinical studies in animal models will provide insights into Vildagliptin's pharmacokinetics and pharmacodynamics when delivered via the pulsincap system. The implications extend beyond diabetes management; methodologies used in this study can be adapted for chronomodulated delivery of other medications targeting diseases with circadian variability such as hypertension, asthma, and cancer. By leveraging chronotherapy principles, healthcare providers can achieve more precise disease management strategies that improve patient outcomes and quality of life.

2. MATERIALS AND METHODS

Materials

The drug Vildagliptin, provided by Dhanuka Laboratories Limited, Old Manesar Road, Village Mohammadpur, Gurgaon, Haryana, India is utilized in our study. The materials employed in the chronomodulated drug delivery system included Eudragit L-100 for controlled release, calcium chloride as a cross-linking agent, and polyvinyl alcohol as a stabilizer. Solvents such as ethanol, methanol, chloroform, and distilled water were used for solubility studies. Buffers and pH adjusters, including sodium phosphate, hydrochloric acid, and sodium bicarbonate, were incorporated to ensure stability. Tween 80 served as a surfactant, while potassium bromide was utilized for Fourier-transform infrared spectroscopy. These materials were essential for the development and evaluation of the system.

Preformulation Studies

Solubility analysis

The solubility of Vildagliptin was determined using the equilibrium solubility method. An excess amount of the drug was added to individual test tubes containing 10 mL of various solvents, including distilled water, ethanol, methanol, dimethyl sulfoxide and phosphate-buffered saline .The test tubes were sealed and agitated on an orbital shaker (Remi, India) at 25°C ± 2°C for 24 hours to achieve equilibrium. The suspensions were then centrifuged at 3000 rpm for 10 minutes, and the supernatant was carefully collected and filtered through a 0.45 µm membrane filter. The concentration of Vildagliptin in each filtrate was analyzed using a UV-visible spectrophotometer at the λmax of 210 nm. All measurements were conducted in triplicate, and the mean solubility values were reported. This analysis provided essential data for optimizing the formulation parameters of the developed chronomodulated drug delivery system [6].

Melting Point

The melting point of Vildagliptin was analyzed using the open capillary method with Thiele's tube. A small quantity of Vildagliptin was placed in a thin-walled capillary tube that was 10-15 mm long and had an inside diameter of approximately 1 mm, with one end closed [7].

Drug-excipient compatibility studies

Fourier Transform Infrared

The compatibility of Vildagliptin with the excipients used in the formulation was analyzed using Fourier Transform Infrared spectroscopy (DRS8000Shimadzu IR Affinity-1). The spectra were recorded by the KBr pellet method. 2 mg of the sample (Vildagliptin, polymer, or their physical mixtures) was mixed with 200 mg of potassium bromide (spectroscopic grade) and compressed into a transparent pellet using a hydraulic press under vacuum. The FTIR spectra were scanned in the wavelength range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1} [8].

Differential Scanning Calorimetry

Differential Scanning Calorimetry is a fast and reliable method for understanding polymorphic transitions and screening drugs and polymers for compatibility, as well as obtaining information about possible interactions. The Differential Scanning Calorimetry analysis of pure Vildagliptin, Eudragit L-100, and their mixture was conducted using a Mettler Toledo differential scanning calorimeter to determine any potential interactions between Vildagliptin and the polymer [9].

Absorption maxima of Vildagliptin

UV-visible spectrophotometer (systronix-2022) is used to determine the lambda max (absorption maxima) of a substance [10]**.**

Formulation Development

Box-Behnken Design was used to systematically investigate the influence of independent variables on the dependent parameters. Seventeen batches based on the Box-Behnken Design were synthesized according to the design outline generated by Design-Expert® software (Version 8.0.6, Stat-Ease)[11].

Table 1: Variables and their levels used in BBD for Vildagliptin microspheres development

Independent variables	**Coded levels of variables**		
	–1	**0**	**+1**
X_1= **Polymer(%w/w)**	3	4.5	6
X_2= **Calcium ion concentration (%w/v)**	10	15	20
X_3= **Stirrer Speed(rpm)**	1000	1500	2000
Dependent variables			
Y_1= Particle size(μm)	Minimize		
Y_2= Entrapment efficiency(% w/w)	Maximize		

Pulsincap drug delivery system

To prepare the Pulsincap drug delivery system, formaldehyde-treated hard gelatin capsules were initially obtained. The bodies and caps of these capsules were then separated manually. Microspheres containing an amount of Vildagliptin equivalent to 50 mg were filled into the capsule bodies. Finally, the capsules were capped using soluble gelatin caps to complete the assembly of the PulsinCap drug delivery system [12].

Particle size distribution

The particle size distribution was determined using a laser diffraction particle size analyzer, which operates on the principle of light scattering. The sample was prepared by dispersing an appropriate amount of the formulation in a suitable dispersant, such as distilled water, and subjected to mild agitation or sonication to ensure proper dispersion. The dispersed sample was then introduced into the particle size analyzer, which measured the scattering of light as it passed through the particles. The scattered light was detected, and the data was used to calculate the particle size distribution. The results were presented as a size distribution curve (intensity percentage versus particle size), along with the cumulative undersize curve to indicate the percentage of particles below a specific size [8].

Evaluation of pulsincap drug delivery system

Weight variation

10 capsules were chosen at random from each batch and weighed individually.

Drug content

This test was done to ensure that Equivalent weight of microspheres introduced into the capsule was within the pharmacopoeia limit (95-105%). Microspheres (equivalent to 50 mg of Vildagliptin) were immersed in 50 mL of 0.1 N HCL for 30 minutes before sonication using a probe sonicator (Model 275 T, Crest Ultrasonics Crop, Trenton, USA) for 10 minutes to break the microspheres and facilitate extraction of the drug. The solution was centrifuged using a centrifuge (Phoenix CD-0412-50 Gmbh, Germany) and was filtered. The clear supernatant solution was analyzed spectrophotometrically at 210 nm [13].

Stability Studies

To conduct the stability study for Vildagliptin Pulsincap formulations, the samples were prepared in their final packaging, ensuring uniformity and homogeneity. These samples were then placed in controlled stability chambers set at specified temperature and humidity conditions. For accelerated stability studies, the formulations were sampled at 0, 1, 2, 3, and 6 months. For long-term studies, they were sampled at 0, 3, 6, 9, 12, 18, and 24 months, and for intermediate studies, at 0, 3, and 6 months [14-15].

3. RESULTS AND DISCUSSION

Preformulation Studies

Solubility analysis*:* The solubility of Vildagliptin was evaluated in five different solvents: distilled water, ethanol, methanol, dimethyl sulfoxide and phosphate-buffered saline.The results presented in Table 3 indicate that Vildagliptin displays distinct solubility profiles across these solvents. The highest solubility was found in distilled water, with a concentration of 3.5 mg/mL, equivalent to 35.0 mg in a 10 mL solution. Dimethyl Sulfoxide also showed considerable solubility at 2.0 mg/mL (20.0 mg in 10 mL), while PBS exhibited moderate solubility at 1.8 mg/mL (18.0 mg in 10 mL). In contrast, ethanol and methanol demonstrated lower solubility, with concentrations of 1.2 mg/mL (12.0 mg in 10 mL) and 1.0 mg/mL (10.0 mg in 10 mL), respectively.

Table 2: Solubility of Vildagliptin in Various Solvents

Solvent	Vildagliptin Concentration (mg/mL)	Solubility (mg/10 mL)
Distilled Water	3.5	35.0
Ethanol	1.2	12.0
Methanol	1.0	10.0
Dimethyl Sulfoxide	2.0	20.0
Phosphate-Buffered Saline	1.8	18.0

Melting point

The melting point of Vildagliptin was determined using the open capillary method with Thiele's tube. The observed melting point was found to be 152°C. This result is in compliance with the reported value for Vildagliptin, confirming the purity and identity of the sample analyzed.

Drug-excipient compatibility studies

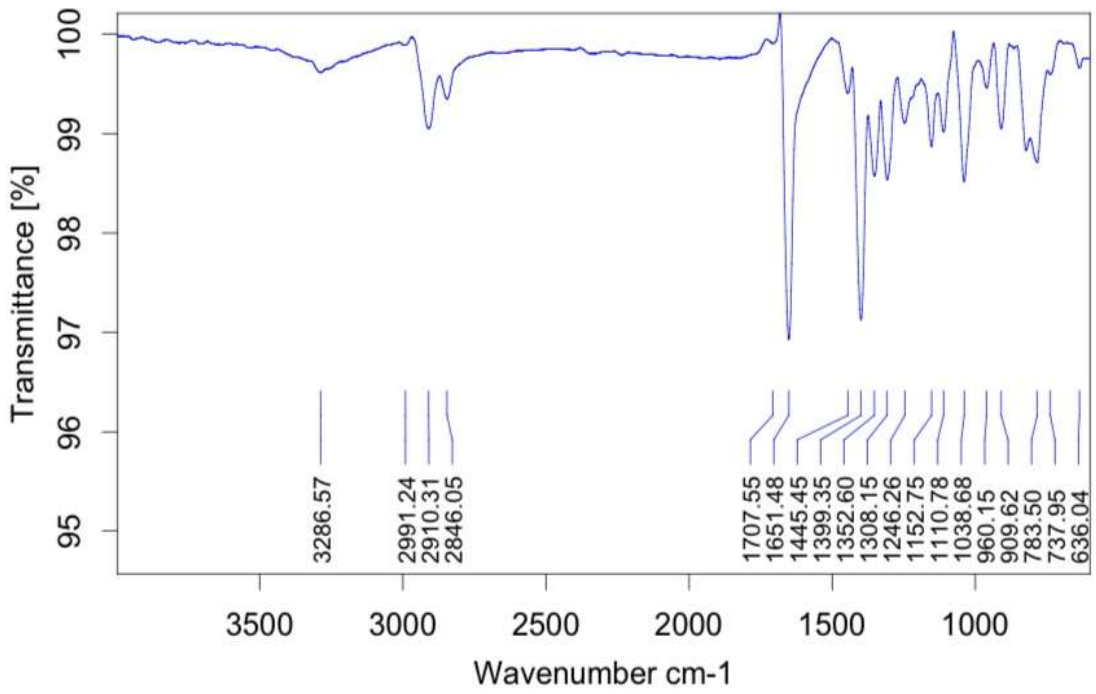


Fig 1. FTIR Spectrum of Vildagliptin

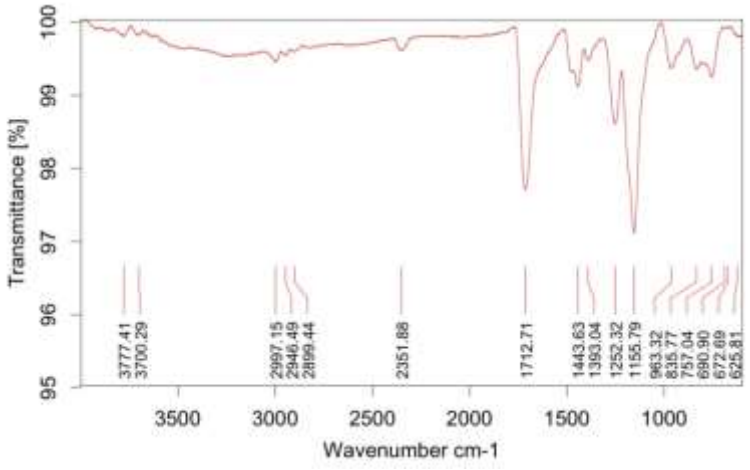


Fig 2. FTIR Spectrum of Eudragit L-100

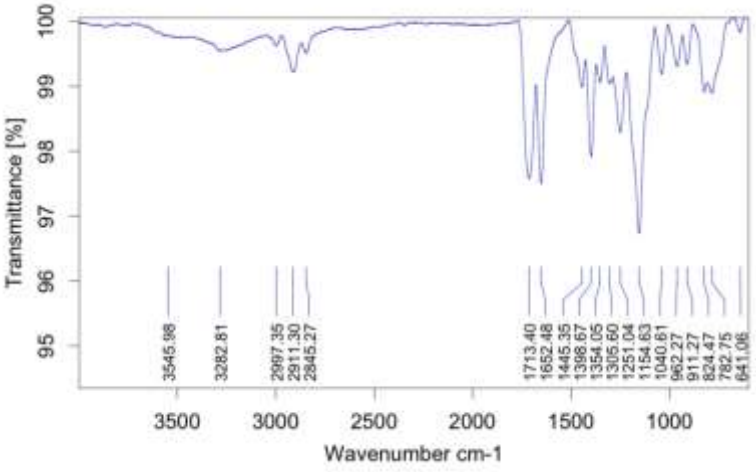


Fig 3. FTIR Spectrum of Physical Mixture of Eudragit L-100 and Vildagliptin

No significant shifts or disappearance of major peaks were observed, suggesting no strong chemical interaction and confirming compatibility of drug and polymer in the microsphere formulation.

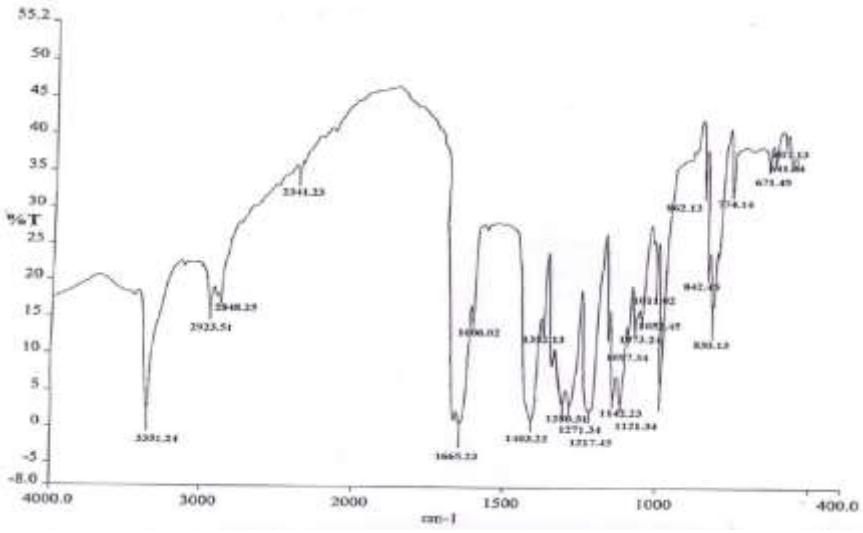


Fig 4. FTIR Spectrum of Vildagliptin Microspheres

The FTIR spectrum of the optimized vildagliptin microspheres shows characteristic peaks of both vildagliptin (e.g., 3351.24 cm^{-1} for N-H/O-H stretch, 1665.23 cm^{-1} for C=O stretch) and Eudragit L-100 (e.g., ester C=O at 1606.02 cm^{-1}), indicating presence of both components.

Differential scanning calorimetry

The differential scanning calorimetry thermogram indicated that Vildagliptin exhibited a sharp endothermic peak at 152.82°C. This sharp peak indicating the presence of a stable crystalline structure for Vildagliptin.

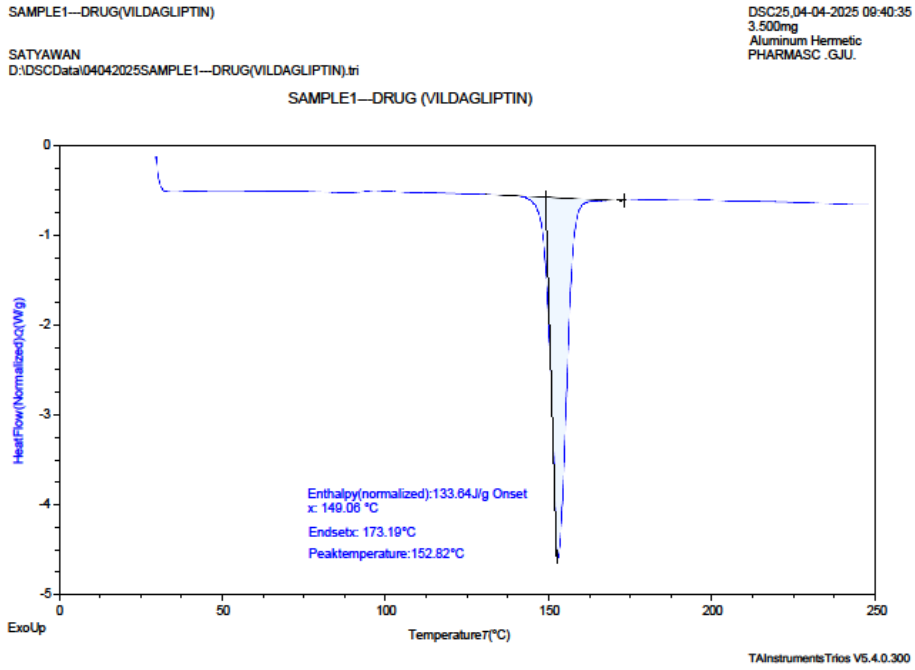


Fig.4 DSC Thermograph of Vildagliptin

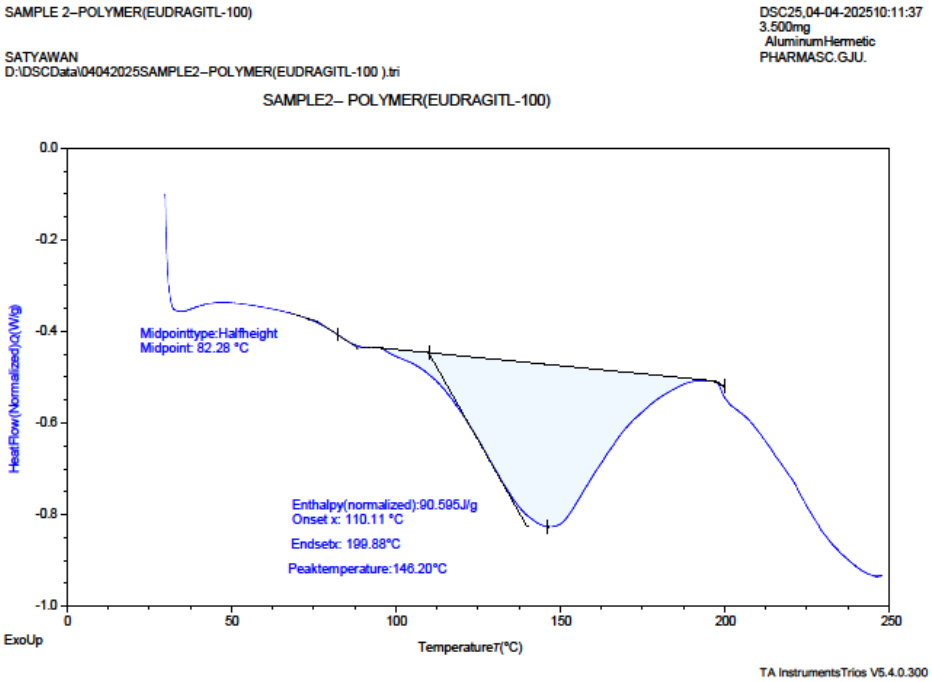


Fig 5. DSC Thermograph of Eudragit L-100

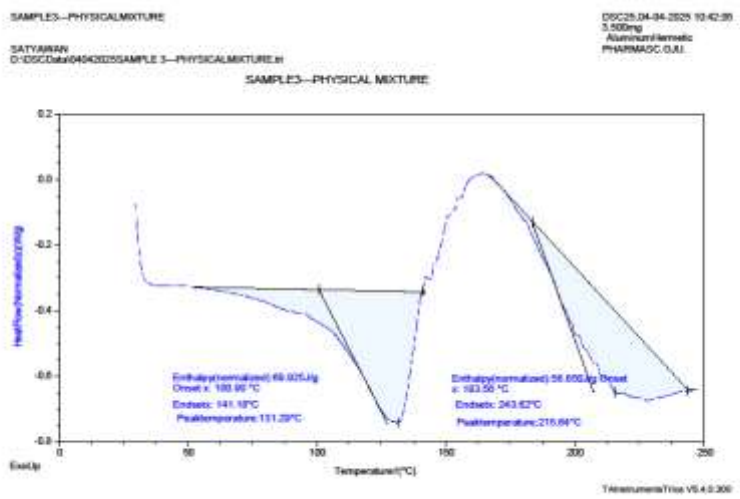


Fig 6. DSC Thermograph of Physical mixture of Vildagliptin Drug and Eudragit L-100

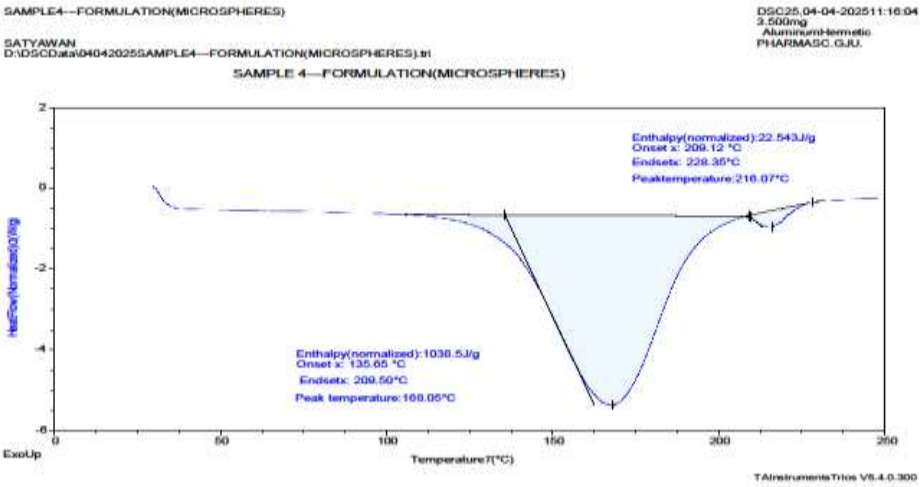


Fig 7. DSC Thermograph of Vildagliptin microspheres Formulation

Absorption maxima of Vildagliptin

The λmax of the Vildagliptin was found to be 210 nm. This is well within the limits of the drug specification as per IP.

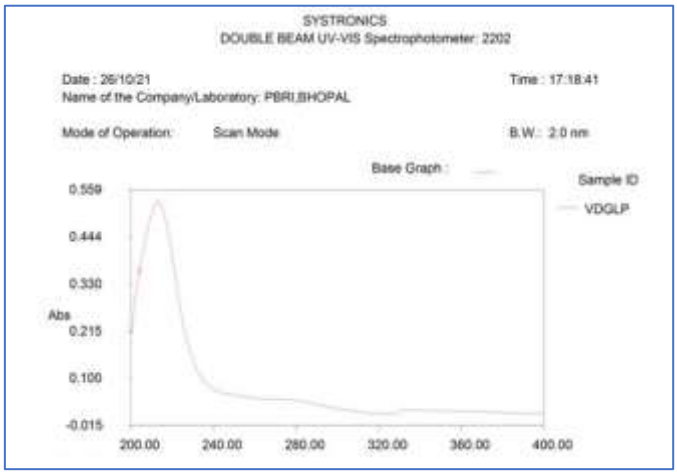


Fig. 8Absorption maxima of Vildagliptin

Particle size distribution

The particle size distribution of the optimized formulation, as shown in the figure 4, indicates a unimodal distribution with a peak intensity centered around 278 µm. This correlates well with the predicted and experimental values from the table, which are 278.74 µm and 277.92 µm, respectively, with a minimal bias of 0.29%. The intensity percentage distribution highlights a consistent and narrow size range, suggesting homogeneity in the particle size of the formulation. The green cumulative undersize curve further supports a well-defined particle size distribution, with most particles falling within the desired size range. These results validate the accuracy of the optimization process and confirm that the formulation meets the targeted particle size requirements.

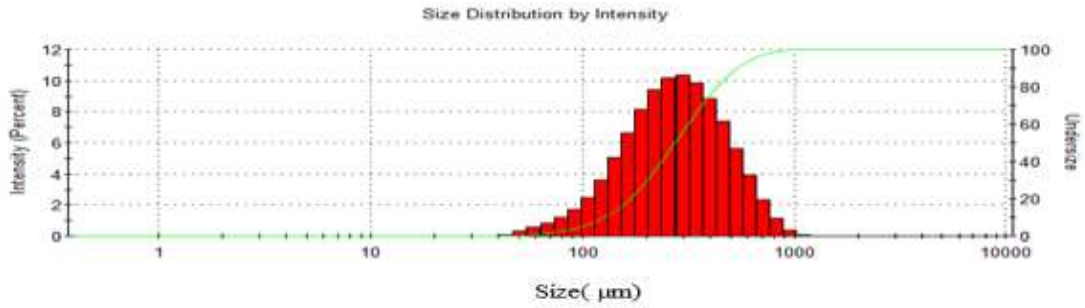


Fig. 9 Particle size distribution of optimized formulation

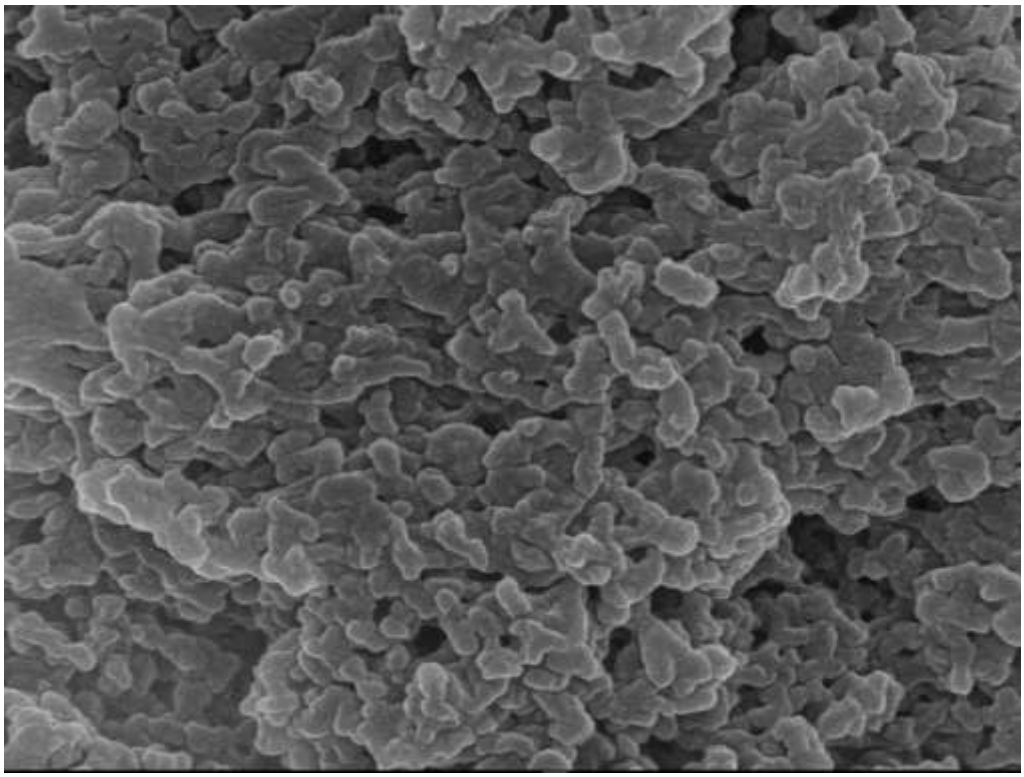


Fig 10. Scanning electron microscopy (SEM) image of Vildagliptin-loaded microspheres

The microspheres formed by this method were well-defined, compact, smooth particles which exhibit a spherical shape with a smooth surface, indicating efficient polymer coating and uniform encapsulation. The absence of surface cracks or pores suggests structural integrity ideal for enteric and controlled release applications.

Pulsincap system

Weight variation

The results of the formulation analysis (Table 4) revealed consistent weights and drug content across all three formulations (F1, F2, and F3). The weight of the empty capsules ranged between 75.22 ± 0.18 mg and 75.95 ±

0.31 mg, showing minimal variation. The weight of the microspheres equivalent to 50 mg of vildagliptin varied among formulations, with F1 being the highest at 70.07 ± 0.15 mg and F2 the lowest at 59.59 ± 0.11 mg. All formulations contained a hydrogel plug weighing approximately 100 mg, which contributed to the total capsule weight. The total weight of the capsules was highest for F1 at 245.43 ± 0.51 mg and lowest for F2 at 234.81 ± 0.50 mg. Drug content was above 98% for all formulations, with F1 showing the highest drug content (99.31 ± 1.36%), indicating excellent encapsulation efficiency. These results confirmed that all formulations were consistent and suitable for further analysis.

Table 3: Weight variation and drug content of Pulsincap system

Formulation No.	Weight of Empty Capsule (mg)	Weight of Microspheres Equivalent to 50 mg Vildagliptin (mg)	Weight of Hydrogel Plug (mg)	Total Weight of Capsule (mg)	Drug Content (%)
F1	75.36±0.25	70.07±0.15	100±0.11	245.43±0.51	99.31±1.36
F2	75.22±0.18	59.591±0.11	100±0.21	234.811±0.5	98.54±3.74
F3	75.95±0.31	67.78±0.42	100±0.13	243.73±0.8	98.45±2.13

Release kinetic of pulsincap system

The *in vitro* drug release study of the Pulsincap system demonstrated distinct release profiles for formulations F1, F2, and F3 over 18 hours. Formulation F1 exhibited the fastest drug release, reaching nearly 100% by the 12th hour, indicating a more immediate release mechanism. In contrast, F2 and F3 showed slower and more sustained drug release, with F2 slightly surpassing F3 in the percentage of drug released at each time point. These results suggested that the formulations were capable of providing controlled release patterns, with F2 and F3 being more suitable for prolonged drug delivery. The differences in release rates could be attributed to variations in formulation components, such as polymers or excipients, affecting drug release kinetics. This study confirmed that the Pulsincap system could be tailored for controlled or immediate drug release based on formulation design.

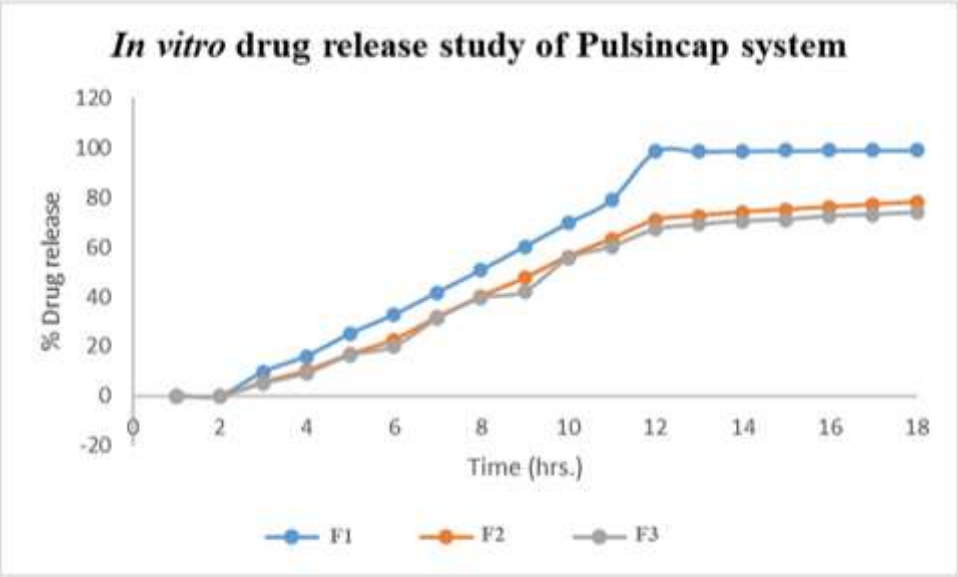


Fig 11. *In vitro* Drug Release curve of Pulsincap system

Table 4: Release kinetic of pulsincap system

Formulation	Model	Kinetic Parameter Values
Pulsincap system	Zero Order	$R^2 = 0.985$
	First Order	$R^2 = 0.750$
	Higuchi	$R^2 = 0.920$
	Korsmeyer-Peppas	$R^2 = 0.769$

The kinetic parameter values for the Pulsincap system indicate varying degrees of fit for different release models [16-18]. The Zero Order model, with an R^2 value of 0.985, shows the highest degree of correlation, suggesting that the release of the drug from the Pulsincap system is best described by a constant release rate over time. The Higuchi model, with an R^2 of 0.920, also provides a good fit, indicating that the release follows a diffusion-controlled mechanism. In contrast, the First Order model, with an R^2 of 0.750, shows a lower correlation, implying that the release rate decreases over time. The Korsmeyer-Peppas model, with an R^2 of 0.769, indicates a moderate fit, suggesting a release mechanism that could involve both diffusion and erosion processes.

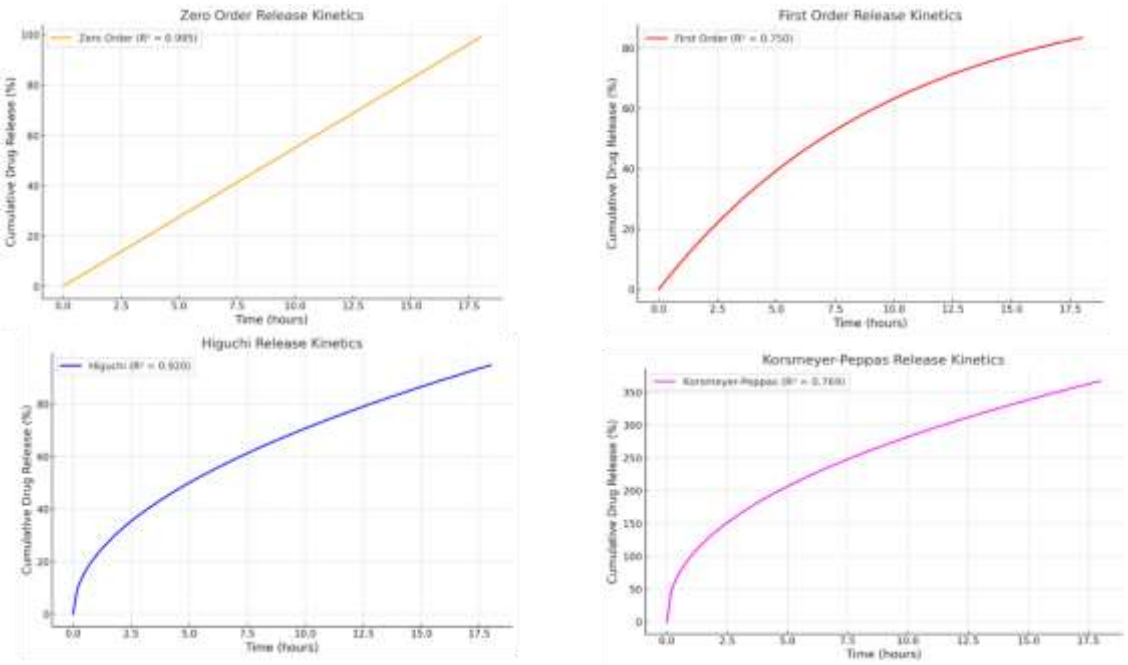


Fig12. Release kinetics of Pulsincap system

Stability studies

Table 5: Stability Study of optimized Pulsincap F1 formulation

Time (Days)	30^0C±2 ^{0}C and 60 ± 5% RH	40^0C±2 ^{0}C and 70 ±5% RH
	In-vitro **release studies (%) 8 hr**	***In-vitro*** **release studies (%) 8 hr**
0	98.12	98.12
30	98.10	97.99
45	97.95	98.18
60	98.05	98.13
90	98.02	98.15

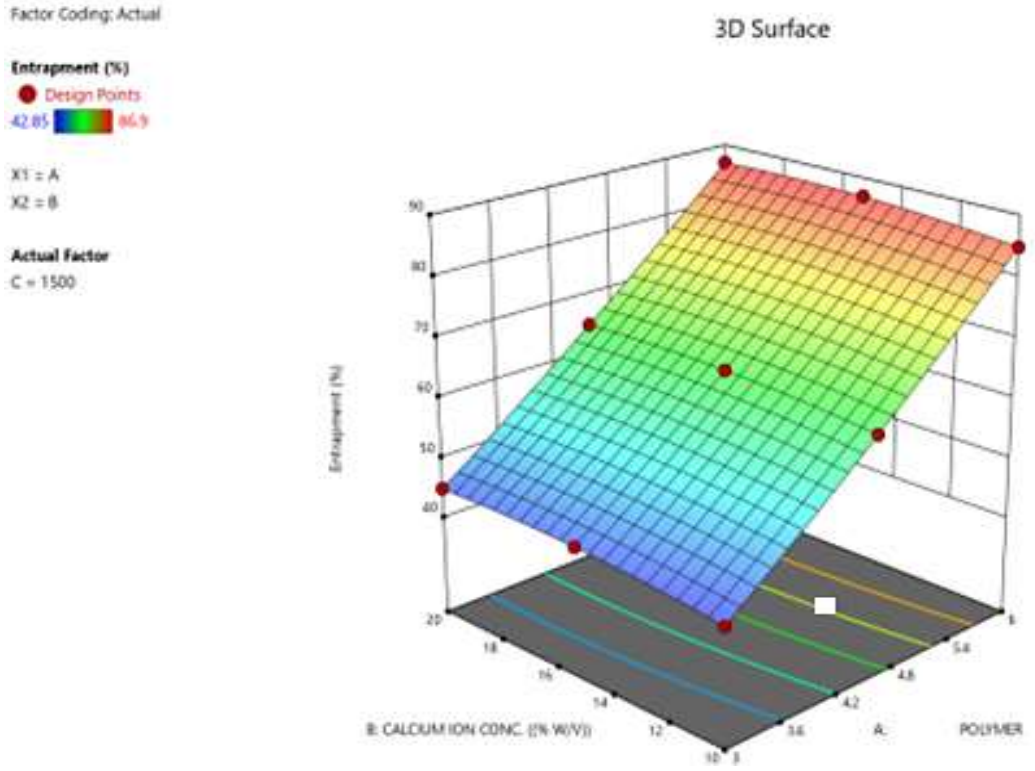
The stability study indicates that there were no significant changes in the physicochemical properties of the formulation and the drug concentration. Throughout the stability study, no significant changes were observed in the physical and chemical characteristics, nor were there significant variations in the in vitro dissolution drug release and lag time. From this stability study, it was also inferred that the formulated PulsinCaps (F1) were stabl [19-20].

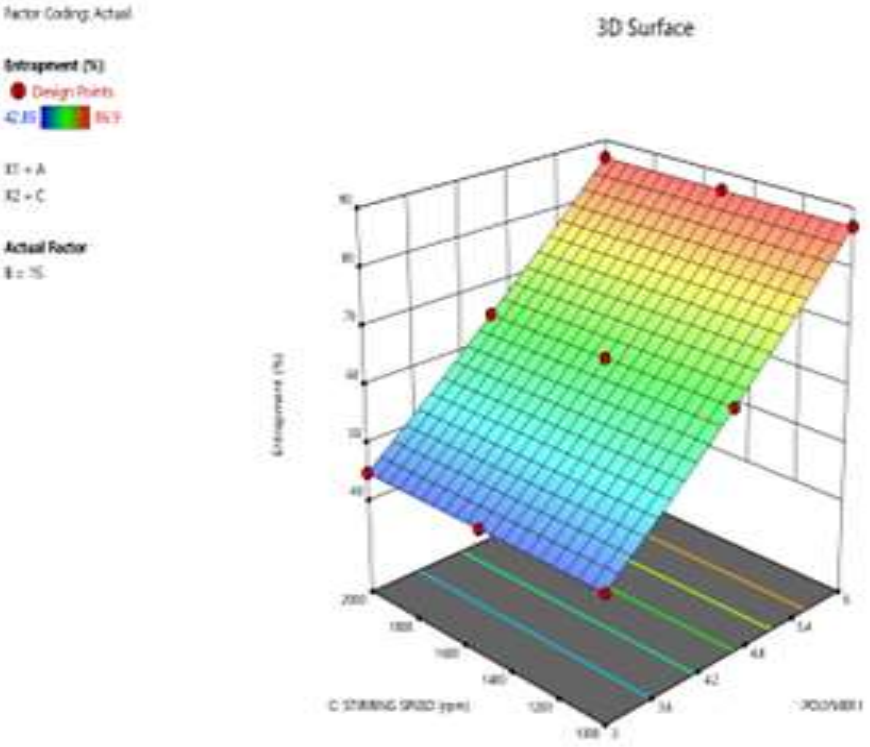
Statistical Assessment of % Entrapment Efficiency (Y2)

The statistical analysis of %EE (Y2) based on polynomial Equation (2) revealed that the factors X1 (drug-polymer ratio) and X2 (concentration of crosslinking agent) had a synergistic effect on Y2, whereas X3 (stirring speed) exhibited an antagonistic effect [21]. The polynomial equation is as follows:

$Y2 = +64.85 + 21.00X1 + 1.00X2 - 0.05X3$ Eq 2

This indicates that increasing the drug-to-polymer ratio (X1) and crosslinking agent concentration (X2) led to a significant improvement in %EE. However, higher stirring speeds (X3) slightly reduced %EE, likely due to destabilization of the system or particle size reduction. Overall, the analysis demonstrated that optimizing the drug-polymer ratio plays a crucial role in enhancing the entrapment efficiency.


Factor Coding: Actual
Entrapment (%)
Design Points
42.85
86.9
X1 = A
X2 = B
Actual Factor
C = 1500
3D Surface
Entrapment (%)
B: CALCIUM ION CONC. ((% W/V))
A: POLYMER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Entrapment (%)
Design Points
X1 = A
X2 = C
Actual Factor
3D Surface

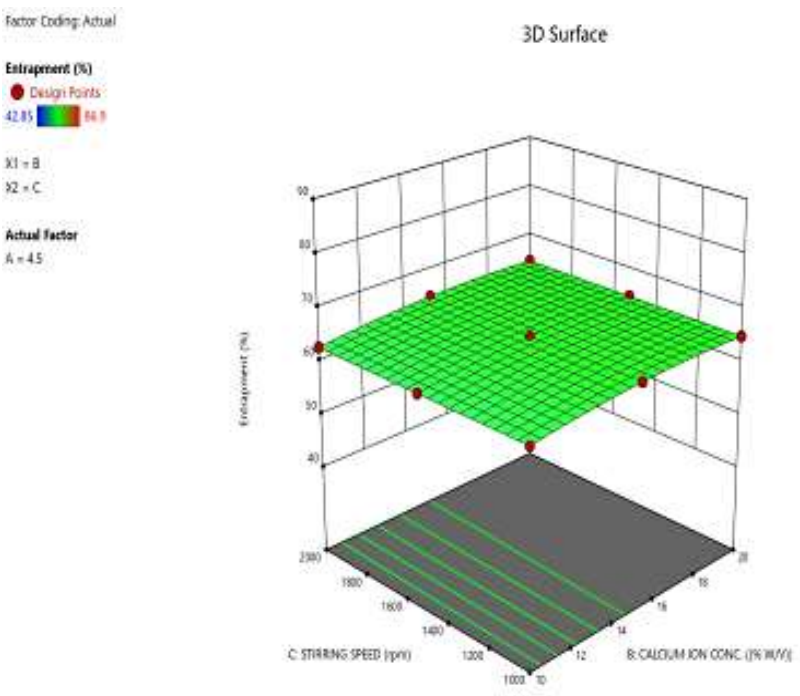

Fig 13. Polymer Concentration and stirring speed in relation to percent entrapment efficiency in 3D Surface response graphs.

4. CONCLUSION

In this study, Vildagliptin microspheres were successfully formulated and evaluated for their potential use in chronomodulated drug delivery systems aimed at managing diabetes. The development process involved optimizing various parameters to ensure the microspheres' efficacy and stability. The prepared microspheres demonstrated controlled release properties, which are essential for synchronizing drug release with the body's circadian rhythms. This controlled release can potentially enhance therapeutic outcomes by ensuring optimal drug levels at the times when they are most needed. The findings from this study indicate that Vildagliptin microspheres loaded pulsincap system could be a promising approach for chronomodulated drug delivery, offering improved patient compliance and better management of diabetes.

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