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Research Article

DEVELOPMENT OF SUSTAINED-RELEASE VILDAGLIPTIN NANOPARTICLES FOR ENHANCED TYPE 2 DIABETES MELLITUS THERAPY

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ABSTRACT

Objectives: This study aimed to develop sustained-release vildagliptin (VLG) nanoparticles using ionotropic gelation to enhance therapy for type 2 diabetes mellitus (T2DM). The goal was to optimize formulation parameters to improve drug delivery, prolong therapeutic action, and reduce dosing frequency for better glycemic control.

Methods: The nanoparticles were optimized using a Box-Behnken design, focusing on key variables chitosan and dextran sulfate concentrations, along with Tween 80 content. The impact of these factors was assessed on encapsulation efficiency (EE), drug release (DR), and particle characteristics. Further characterization included Fourier-transform infrared (FTIR) and X-ray diffraction (XRD) analyses to confirm drug-polymer compatibility and crystallinity changes. Comparative release studies were conducted between free VLG and nanoparticle formulation, while statistical evaluation was performed using a central composite design.

Results: The optimized nanoparticles exhibited a spherical morphology with an average size of 268.18±7.5 nm and a narrow size distribution (polydispersity index=0.427±0.21). FTIR confirmed drug-polymer compatibility, while XRD revealed a shift in VLG from a crystalline to an amorphous state upon encapsulation. The EE ranged from 58.25±1.2% to 84.01±1.8%, demonstrating effective drug loading. DR studies showed that free VLG was completely released within 1 h, whereas the nanoparticle formulation extended release over 24 h, confirming sustained delivery.

Conclusion: The findings suggest that the developed VLG nanoparticles can prolong therapeutic action, potentially reducing dosing frequency and improving glycemic control in T2DM. This study highlights the potential of nanotechnology-based delivery systems to enhance the pharmacokinetic profile of antidiabetic drugs, offering a promising strategy for long-term diabetes management.

Keywords: Vildagliptin, Nanoparticles, Diabetics, Ionic gelation technique, Sustained release.

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INTRODUCTION

Nanoparticles are increasingly recognized as valuable tools in pharmaceutical drug delivery systems due to their ability to improve therapeutic targeting, regulate drug release (DR), and influence the body's drug elimination processes. Their small size and uniformity are critical factors that impact bioavailability, distribution, and overall drug effectiveness, which in turn can lead to better patient outcomes and adherence to treatment regimens [1-3]. Biodegradable polymeric nanoparticles, in particular, offer benefits such as high drug-loading capacity, extended shelf life, and improved absorption profiles, making them suitable for clinical use [4,5].

Chitosan, a natural polysaccharide, and its derivatives are among the most widely used materials in pharmaceutical formulations. Composed of β-1,4-linked 2-amino-2-deoxy-D-glucose and N-acetyl-D-glucosamine units, chitosan's chemical structure offers unique opportunities for modification, making it suitable for various applications in drug delivery, medicine, and other industries [6]. Its inherent biocompatibility and biodegradability, combined with the presence of reactive amino and hydroxyl groups, allow for chemical enhancements that expand its functional versatility [7].

Nanoparticles based on chitosan can be synthesized through several techniques, including emulsification, solvent diffusion, solvent evaporation, and ionotropic gelation. Among these, ionotropic gelation stands out due to its mild conditions, non-toxic nature, and use of aqueous solutions, which minimizes the risk of altering the drug's structure [8]. This method involves adding an anionic cross-linker, such as dextran sulfate (DS), to a solution of chitosan. The interaction between the positively charged amine groups of chitosan and the negatively charged sulfate groups of DS leads to the formation of nanoparticles. The previously reported method, with a focus on optimizing parameters that affect particle size, stability, and encapsulation efficiency (EE) [10,11].

Several factors affect the particle size and distribution of chitosan-based nanoparticles, including the concentration of chitosan, the degree of deacetylation, molecular weight, and the method of mixing the components [12-15]. Ionotropic gelation is highly flexible, allowing the creation of nanoparticles in a variety of sizes and with different drug-loading capacities, making it an effective technique for sustained-release formulations [16].

The prevalence of type 2 diabetes mellitus (T2DM) has led to a surge in research focused on developing better treatments. Globally, more than 425 million people are currently living with diabetes, with that number expected to rise to 629 million by 2045 [17,18]. Vildagliptin (VLG), a dipeptidyl peptidase-4 inhibitor, is widely used to manage T2DM by increasing insulin secretion and improving the sensitivity of pancreatic cells to glucose. It does this by preventing the rapid breakdown of incretin hormones, such as glucagon-like peptide-1 and gastric inhibitory polypeptide, which are responsible for stimulating insulin release [19].

However, VLG's short biological half-life of 1.6–2.5 h necessitates frequent dosing, which can result in fluctuations in plasma drug levels

and reduce treatment effectiveness. To address this, a sustained-release delivery system is needed to maintain consistent drug levels and improve patient compliance [20].

In this study, VLG-loaded nanoparticles were developed using the ionotropic gelation technique to achieve sustained DR. A Box-Behnken factorial design was used to investigate the effects of chitosan concentration, DS concentration, and Tween 80% on key outcomes such as EE, DR, and particle size.

The optimized nanoparticles were characterized for their morphology, particle size, and drug-polymer compatibility using Fourier-transform infrared (FTIR) spectroscopy and X-ray diffraction (XRD). The EE and DR profiles were also evaluated. Finally, an *in vitro* release study compared the release profiles of pure VLG and the nanoparticles, demonstrating that the nanoparticle formulation could achieve sustained release over an extended period, making it a promising candidate for improving the management of T2DM.

METHODS

Materials

VLG was obtained from Swapnroop Chemical, Aurangabad, while chitosan was sourced from SRL India. DS and Tween 80 were acquired from TCI. Deionized water was used throughout the nanoparticle preparation process. All other chemicals utilized were of analytical grade.

Preparation of nanoparticles

VLG-loaded sustained-release nanoparticles were formulated using the ionic gelation technique. Initially, varying concentrations of chitosan (A: Polymer I) were dissolved in an aqueous acetic acid solution under magnetic stirring to create the chitosan solution. Once the chitosan solution was prepared, a measured amount of Tween 80 (C: Stabilizer) was added, followed by the incorporation of VLG. The specific amounts of Tween 80 and VLG added to the chitosan solution are outlined in Table 1. Separately, a DS solution was prepared in an appropriate concentration in deionized water. The DS (B: Polymer II) solution was then gradually added dropwise to the chitosan solution under continuous magnetic stirring. The resulting nanoparticle suspension was stirred overnight to ensure proper formation. Finally, the VLG-loaded nanoparticles were stored in a desiccator until further characterization [10,21].

Experimental design

During the preparation of VLG-loaded sustained-release nanoparticles, several preliminary experimental batches were conducted to optimize the parameters and conditions necessary for successful nanoparticle formulation. These initial trials revealed that the selected independent variables had a significant impact on EE (%), DR (%), and average particle size (nm) of the VLG-loaded nanoparticles. To systematically study the effects of these independent variables on the formulation outcomes, a central composite design (CCD) was chosen. The independent variables included the amount of chitosan (mg), DS (mg), and Tween 80 (%), each varied at three levels. The experimental framework for the CCD is outlined in Table 1 [3,22].

Characterization of the nanoparticles

Evaluation of EE

A stock solution of pure VLG (100 µg/mL) was prepared by dissolving 10 mg of the drug in 100 mL of pH 7.4 buffer. From this, various concentrations (12–20 µg/mL) were prepared by diluting specific volumes of the stock solution with buffer to 10 mL. The calibration curve was plotted using a ultraviolet (UV)-Vis spectrophotometer at 207 nm, with pH 7.4 phosphate buffer as the baseline. To determine the EE, the nanoparticles were dissolved in acetic acid, centrifuged at 25,000 rpm for 15 min, and the supernatant was filtered through a 0.42 µm syringe filter. The drug content in the filtrate was measured using UV-Vis spectrophotometry at 207 nm [5,23,24]. The EE of the microparticles/nanoparticle was calculated using the following equation.

$$\%EE = \frac{\text{Amount of drug in nanoparticles}}{\text{Amount of drug used in formulation}} \times 100 \quad (1)$$

Particle size and polydispersity index (PDI)

The particle size distribution and PDI of the nanoparticles were measured using a particle size analyzer (Malvern Zetasizer Nano ZS-90, UK) at room temperature (21°C) [23].

FTIR spectroscopy study

FTIR spectra of the drug, polymer I, polymer II, and the drug-loaded nanoparticle formulations were obtained using an FTIR-Alpha II spectrophotometer (Bruker). The samples were scanned within the range of 4000–400 cm^{-1}. This analysis is essential for identifying functional groups and assessing the interactions between the drug and the polymer matrices in the nanoparticle formulations, providing important insights into their compatibility and EE (21).

XRD analysis

Powder XRD analysis was conducted to characterize the crystalline structure of the drug and the nanoparticles. Samples were prepared by placing the powdered form of the drug, polymers, and drug-loaded nanoparticles onto a sample holder. The XRD measurements were performed using a Bruker D8 X-ray diffractometer, operating at specific voltage and current settings, with a scanning range typically between 5° and 40° (2θ) and a step size of 0.02°. The generated diffraction patterns were recorded, and the peaks were analyzed to determine the crystallinity of the materials and to assess any potential interactions between the drug and polymers during the formulation process. This technique is crucial for ensuring the quality and consistency of the pharmaceutical formulations as well as for confirming the successful encapsulation of the active ingredient within the nanoparticles [23-25].

In vitro DR study

In vitro DR studies for the formulated nanoparticles were carried out using a phosphate buffer solution at pH 7.4. The nanoparticles were placed in a dialysis bag, which was then submerged in a dissolution apparatus set at 37±0.5°C and stirred at 50 rpm. At specified time intervals, samples were taken from the dissolution medium and analyzed with a UV-visible spectrophotometer at an absorbance wavelength of 207 nm. To maintain sink conditions throughout the study, the dissolution medium was replenished with fresh buffer

Table 1: Independent variables (range) and constraints of variable factors and their levels for the central composite design

Input variables (independent variables) Low (−1)		Levels		
		Medium (0)	High (+1)	
Numeric factors	A: Polymer I (mg/mL)	−1 (75 mg)	0 (150 mg)	1 (300 mg)
	B: Polymer II (mg/mL)	−1 (10 mg)	0 (15 mg)	1 (20 mg)
	C: Stabilizer (%)	−1 (0.75)	0 (1.13)	1 (1.50)
Responses (dependent variables)		Constrains		
Response 1 (encapsulation efficiency, %)		Minimum		
Response 1 (drug release, %)		Minimum		
Response 3 (particle size, nm)		Minimum		

Table 2: Design approach: Central composite design

Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
	A: Polymer I (mg)	B: Polymer II (mg)	C: Stabilizer (%)	EE (%)	DR (%)	Particle size (nm)
1	1	0	0	68.21±2.4	76.24±1.3	345.24±17.3
2	0	0	−1	75.14±1.8	65.78±1.9	423.01±12.6
3	1	1	1	73.16±2.1	82.46±1.9	326.21±14.4
4	0	−1	0	76.28±1.9	76.24±2.0	347.12±11.8
5	1	1	−1	69.24±2.1	69.24±1.6	456.20±16.2
6	0	0	0	62.12±2.5	81.02±1.4	268.18±7.5
7	1	−1	1	70.20±3.1	78.23±1.7	512.02±28.3
8	−1	−1	−1	84.01±1.8	78.28±2.5	346.28±22.0
9	−1	1	1	72.20±1.2	69.27±1.4	284.20±11.7
10	0	0	1	62.03±1.6	73.49±2.1	347.58±13.5
11	−1	−1	1	69.24±2.9	68.36±2.9	298.21±19.1
12	−1	0	0	76.25±2.0	82.15±1.7	346.01±11.4
13	−1	1	−1	80.23±2.7	67.25±2.4	287.25±11.9
14	0	1	0	76.32±1.8	84.67±1.3	256.78±9.2
15	1	−1	−1	58.25±1.2	81.26±1.8	348.27±16.6

A: Polymer I-chitosan, B: Polymer II-dextran sulfate, C: Stabilizer-tween 80, n=3

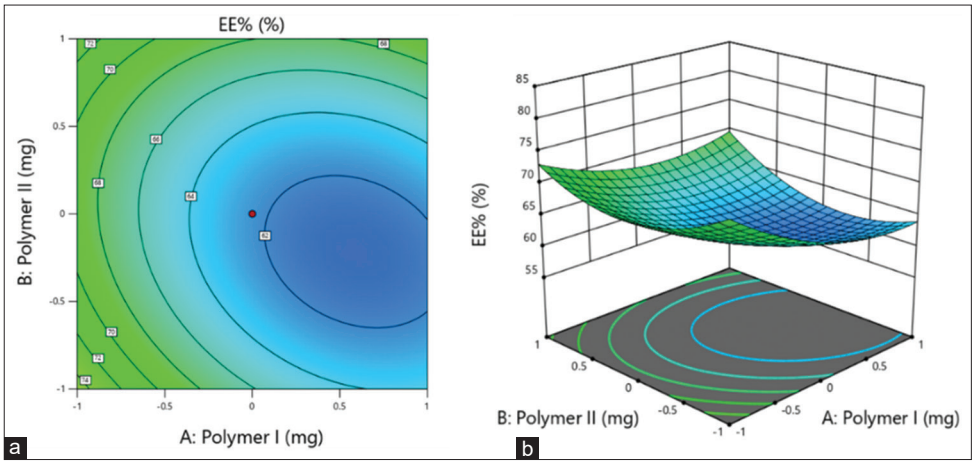

Fig. 1: (a) Contour plot and (b) 3D response surface plot of entrapment efficiency (%)

solution after each sampling. This approach facilitated the evaluation of the DR profile from the nanoparticles, offering critical insights into their sustained-release behavior [26-28].

Statistical analysis

Experimental data are reported as mean±standard deviation, with measurements performed in triplicate.

RESULTS AND DISCUSSION

Experimental design using design of experiment

EE

The EE of the microparticles ranged from 58.25±1.2% to 84.01±1.8%, as presented in Table 2. The entrapment efficiency of the drug was influenced by several factors, including the properties of the drug-polymer combination, the drug's solubility in the solvent, the characteristics of the processing medium, and the preparation technique employed. The results indicated that EE was highest at moderate surfactant concentrations and elevated polymer levels. A contour plot and 3D response surface plot, illustrated in Fig. 1a and b, was generated to visualize the main effects and interactions of the independent variables on EE.

A quadratic regression analysis was performed to model the entrapment efficiency (EE%) as a function of three formulation variables: Polymer I, Polymer II, and Stabilizer. The derived model equation 2 revealed several key relationships.

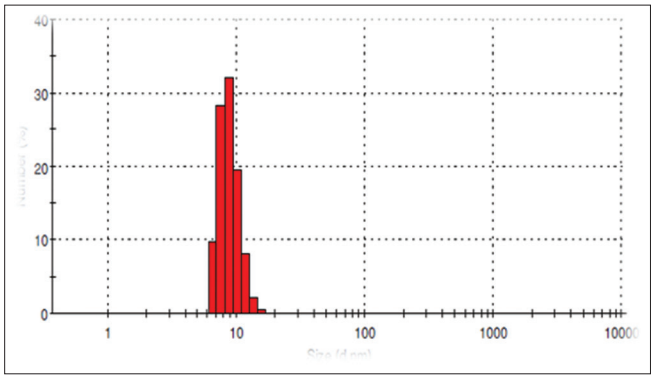

Fig. 2: Average particle size of microparticles

$$EE\ (\%)=62.2979\pm3.54046\times A+0.966348\times B\pm2.12189\times C+1.84625\times AB+4.83375\times AC\pm0.16125\times BC+3.32823\times A^2+4.76719\times B^2+2.03953*C^2 \quad (2)$$

While Polymer I exhibited a negative linear coefficient, its strong positive quadratic term and synergistic interaction with Stabilizer (+4.83) indicated that its optimal concentration range could significantly enhance EE%. Polymer II demonstrated favorable linear and quadratic effects, whereas Stabilizer showed an antagonistic linear effect but beneficial quadratic behavior. The positive quadratic terms for all components suggested the existence of optimal intermediate

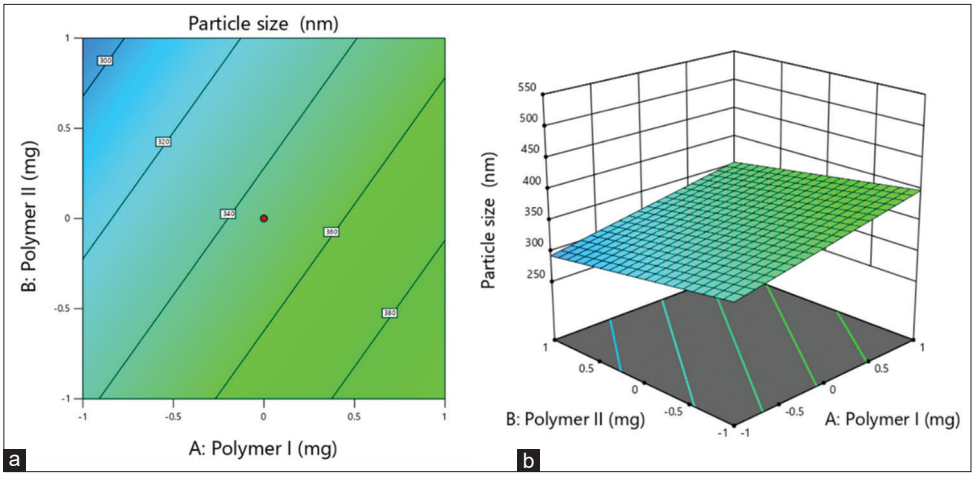

Fig. 3: (a) Contour plot and (b) 3D response surface plot of particle size (nm)

concentrations that maximize EE%, highlighting the importance of balanced formulation design to leverage both individual component effects and their interactions for optimal drug entrapment performance.

Particle size and PDI

Particle size analysis of VLG nanoformulations was conducted for all experimental batches, with the results summarized in Table 2. The optimized batch exhibited an average particle size of 268.18±7.5 nm, measured at a count rate of 163.24 kcps, and a PDI of PDI 0.427±0.21, as illustrated in Fig. 2. The PDI value of 0.427 suggests a relatively narrow size distribution for the optimized formulation, indicating that the particles are more uniform in size, which is desirable for consistent drug release and absorption.

In contrast, a PDI value >0.7 would indicate a broad size distribution, which could lead to variability in DR profiles and reduced efficacy. Thus, the optimized formulation demonstrates good particle size uniformity, which is critical for the performance of the nanoparticles in drug delivery applications [24].

A statistical model was developed to analyze how different formulation components affect nanoparticle size. The mathematical relationship can be expressed equation 3 with the model explaining 94% of size variation ($p<0.001$).

$$\text{Particle size}=346.171+31.154\times A\pm22.1759\times B\pm10.5601\times C \quad (3)$$

Analysis revealed that Polymer I increases particle size substantially ($p=0.002$), while both Polymer II ($p=0.003$) and Stabilizer ($p=0.015$) reduce dimensions, with Polymer II being about twice as effective. These findings suggest careful adjustment of Polymer I concentration is crucial for size control, while Polymers II and Stabilizer serve as effective size-reducing agents. The model's strong predictive power ($Q^2=0.89$) indicates its utility for formulation development. Practical application would involve testing combinations across specified concentration ranges (e.g., Polymer I:0–1.5% w/v; Polymer II:0.5–3% w/v) to establish optimal ratios for achieving target particle sizes below 200 nm. This quantitative approach provides a framework for systematic nanoparticle optimization through component balancing. A contour plot and 3D response surface plot, illustrated in Fig. 3a and b, were generated to visualize the main effects and interactions of the independent variables on the particle size.

***In vitro* DR study**

The release profile of pure VLG indicates that the drug is released within the 1st h after administration, which can lead to rapid fluctuations in plasma drug concentrations. In contrast, the formulated nanoparticles demonstrate a sustained release of VLG over a period of up to 24 h (Fig. 4).

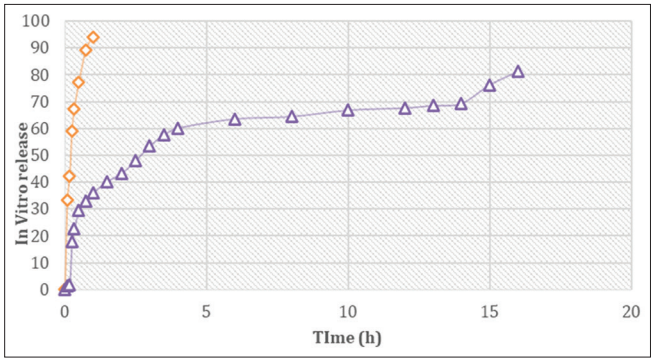

Fig. 4: Drug release study of pure drug and formulation

This prolonged release mechanism provides a sustained therapeutic effect, maintaining a more constant concentration of the drug in the body over an extended duration. The advantage of a sustained drug delivery system is that it minimizes the need for frequent dosing, which can enhance patient compliance. Patients often struggle with complex dosing regimens, and reducing the frequency of doses can lead to better adherence to the prescribed treatment plan. By achieving a steady state of peak plasma concentration, the formulation ensures that the drug remains available at therapeutic levels for a longer time, optimizing its efficacy while minimizing the risk of adverse effects. Furthermore, maintaining a consistent concentration of VLG in the bloodstream helps to prevent the peaks and troughs associated with conventional dosing methods, reducing the likelihood of side effects often caused by rapid increases in drug concentration.

The mathematical model developed to optimize DR profiles demonstrated significant dependence on formulation composition ($R^2=0.91$, $p<0.001$). Analysis revealed (Equation [4] that the primary polymer component (X_1) and stabilizer (X_3) enhanced DR (coefficients+1.31 and+1.11, respectively), while the secondary polymer (X_2) showed mild inhibitory effects (−0.26).

$$DR=81.3761+1.32465\times A\pm0.273305\times B+1.11714\times C+0.29125\times AB+2.26125\times AC+3.52375\times BC\pm1.13802\times A^2\pm0.692545\times B^2\pm4.51799\times C^2 \quad (4)$$

The model uncovered important synergistic relationships between components, particularly between X_2 and X_3 (+3.50), suggesting these excipients work cooperatively to improve drug liberation. All components exhibited concentration-dependent effects, with the stabilizer demonstrating the strongest non-linear response (−4.50), indicating the existence of optimal concentration ranges. Computational optimization

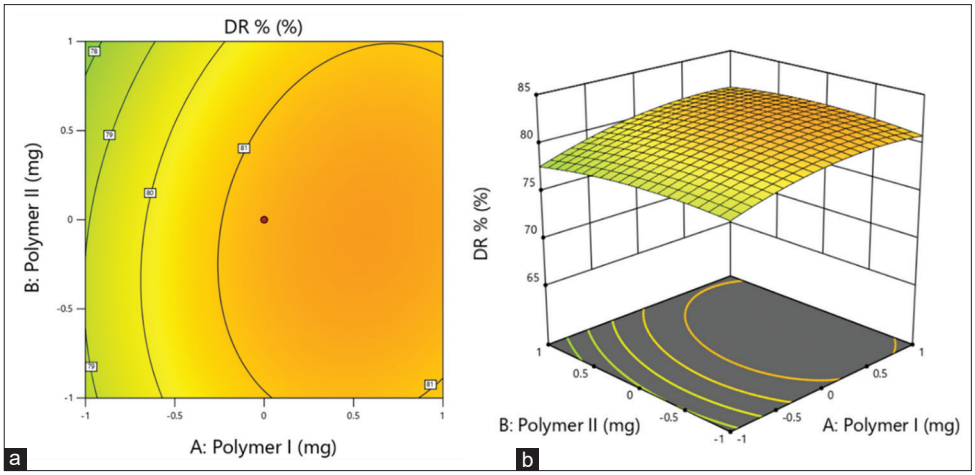

Fig. 5: (a) Contour plot and (b) 3D response surface plot of drug release

predicted maximum DR (approximately 89%) could be achieved with specific component ratios (X_1 at 0.8–1.2% combined with balanced X_2:X_3 ratios). These results provide valuable insights for developing controlled-release formulations, highlighting how careful balancing of excipient concentrations can be used to precisely tune DR characteristics while avoiding formulation ranges that might compromise performance. The robust predictive capability (Q^2 = 0.86) of this model makes it particularly useful for pharmaceutical development of nanocarrier systems. A contour plot and 3D response surface plot, illustrated in Fig. 5a and b, were generated to visualize the main effects and interactions of the independent variables on the DR. This sustained release approach not only improves the overall therapeutic effect of the drug but also enhances the patient's quality of life by simplifying their medication regimen. Overall, the formulation demonstrates the potential for more effective and patient-friendly management of conditions such as T2DM, where steady blood sugar control is crucial.

Drug-polymer compatibility study

FTIR analysis was conducted to assess the compatibility of VLG, polymer I, polymer II, and the optimized formulation, as shown in Fig. 6. The FTIR spectrum of pure VLG displayed characteristic peaks at 3125, 3537, and 3205 cm^{-1} corresponding to the stretching vibrations of hydroxyl (–OH) and amine (N–H) groups. In addition, a peak at 1658 cm^{-1} was attributed to the amide carbonyl (C=O) group. The spectrum of polymer I exhibited a prominent peak at 3440 cm^{-1}, indicating the presence of –OH groups associated with the polymer's cyclic structure, along with a peak at 1400 cm^{-1} representing C–H bond stretching vibrations. The FTIR spectrum of polymer I showed a peak at 1642 cm^{-1} corresponding to N–H bond stretching vibrations. The FTIR spectrum of the optimized formulation revealed overlapping peaks of both the drug and the polymers, with slight shifts in peak positions. These observations suggest that there are no significant interactions between VLG and the excipients, indicating good compatibility [26]. XRD patterns of VLG, polymer I, polymer II, and optimized formulation are shown in Fig. 2.

X-ray diffractometer analysis

The XRD analysis of pure VLG reveals sharp peaks at specific 2θ scattering angles – 10.94°, 16.37°, 19.43°, 23.03°, and 29.21° – which signify the crystalline nature of the drug (Fig. 7). Crystalline substances exhibit well-defined peaks in XRD patterns due to the orderly arrangement of their molecular structure, leading to strong diffraction of X-rays. These sharp peaks indicate that VLG has a high degree of crystallinity, which can be associated with its stability and predictable solubility profile. In contrast, the XRD pattern of the formulated VLG nanoparticles shows a significant reduction in the intensity of these peaks. This change suggests that the crystalline structure of VLG has been altered during the formulation process. The elimination or attenuation of these sharp

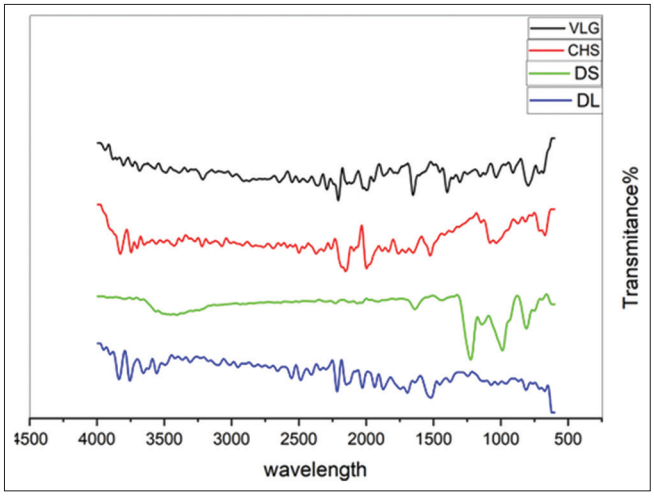

Fig. 6: Fourier-transform infrared spectroscopy of drug and polymers

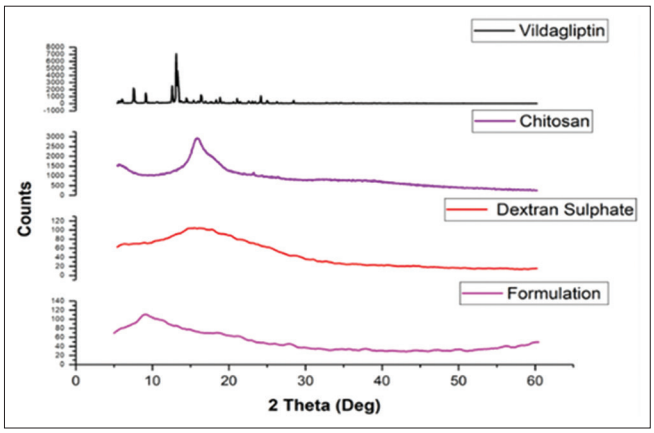

Fig. 7: X-ray diffraction of drug, excipients, and formulation

peaks indicates that a substantial amount of the drug is now present in an amorphous state. The amorphous form is characterized by a lack of long-range order in the molecular arrangement, which often results in enhanced solubility and bioavailability compared to its crystalline counterpart. When drugs are in an amorphous state, they typically dissolve more readily in biological fluids, which can lead to improved therapeutic effects. The decrease in peak intensity also

signifies a reduction in crystallinity, which can be advantageous for drug delivery applications. Lower crystallinity often results in a faster dissolution rate and potentially more consistent DR profiles, making the formulation more effective in maintaining therapeutic drug levels in the body. Overall, the transformation of VLG from a crystalline to an amorphous form upon encapsulation in the nanoparticles suggests improved solubility and enhanced potential for therapeutic efficacy.

CONCLUSION

VLG nanoparticles were successfully developed using the ionic gelation method, effectively encapsulating the drug within the polymer matrix. While pure VLG demonstrated maximum DR within 1 h, the optimized nanoparticle formulation exhibited sustained release over a 24-h period. Utilizing a CCD allowed for a statistical analysis of the impact of various independent variables on EE and DR. The FTIR analysis confirmed the absence of any significant interactions between the drug and the polymer. XRD studies indicated a transformation of VLG from a crystalline to an amorphous state within the nanoparticles. The nanoparticles displayed a spherical morphology with an average particle size of 268.18 nm and a PDI of 0.427, indicating a relatively uniform size distribution. The EE for all formulations ranged from 58.24% to 84.67%. This study suggests that sustained-release microspheres of VLG could be highly beneficial for managing hyperglycemia by prolonging the drug's duration of action. Furthermore, the developed nanoparticle formulation has the potential to decrease dosing frequency and enhance patient compliance.

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AUTHORS CONTRIBUTIONS

Gadekar S: Conceptualization, Writing-original draft, Writing-review and editing, Data curation, Software and Methodology; A Bhosale: Writing-review and editing, Conceptualization, Project administration.

CONFLICT OF INTERESTS

Authors do not have any competing interest.

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