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Original Research Article

FORMULATION AND EVALUATION OF VILDAGLIPTIN LOADED BIO-ADHESIVE MICROSPHERES

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ABSTRACT

The objective of this study was to formulate and evaluate bioadhesive chitosan microspheres of Vildagliptin for sustained drug delivery. Microspheres were prepared by the ionotropic gelation method using chitosan and sodium tripolyphosphate as crosslinking agents. Six different formulations (F1–F6) were developed by varying polymer concentrations. The prepared microspheres were evaluated for percentage yield, entrapment efficiency, particle size, zeta potential, flow properties, and in vitro drug release. Among the formulations, F3 showed the highest entrapment efficiency ($73.32 \pm 0.15\%$) and percentage yield ($72.45 \pm 0.36\%$). In vitro drug release studies demonstrated that the chitosan microspheres could sustain the release of Vildagliptin over 12 hours compared to the immediate release from the plain drug. Kinetic modeling revealed that drug release followed zero-order kinetics and a diffusion-controlled mechanism. The findings suggest that bioadhesive microspheres offer a promising strategy for the controlled delivery of Vildagliptin, potentially enhancing its therapeutic efficacy.

Keywords: Vildagliptin, Bioadhesive microspheres, Chitosan, Ionotropic gelation, Controlled release, Entrapment efficiency, Drug release kinetics.

INTRODUCTION

Diabetes mellitus is a multifactorial metabolic disorder that affects millions globally and is characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes mellitus (T2DM) is the most prevalent form, accounting for more than 90% of diabetes cases worldwide, and is primarily associated with insulin resistance and relative insulin deficiency (Kumar *et al.*, 2019). Long-term uncontrolled diabetes can lead to complications affecting the cardiovascular system, kidneys, eyes, and nervous system, making effective management critical.

In recent years, Dipeptidyl Peptidase-4 (DPP-4) inhibitors have emerged as an important class of oral antihyperglycemic agents. These drugs act by inhibiting the enzyme DPP-4, which is responsible for the degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1). These incretins enhance insulin secretion and suppress glucagon production in a glucose-dependent manner (Drucker *et al.*, 2007). Vildagliptin, a potent and selective DPP-4 inhibitor, has demonstrated clinical efficacy in lowering blood glucose levels, improving β-cell function, and exerting a low risk of hypoglycemia (Ahrén *et al.*, 2004).

However, Vildagliptin has certain pharmacokinetic limitations, including a short biological half-life (~1.5–2 hours) and the need for twice-daily administration, which

can reduce patient adherence and overall therapeutic effectiveness (Sharma *et al.*, 2020). To overcome these challenges, controlled-release drug delivery systems are being extensively investigated to provide sustained drug release, maintain therapeutic drug concentrations, and reduce dosing frequency (Lehr *et al.*, 1996).

Bio-adhesive microspheres, a subset of controlled drug delivery systems, are designed to adhere to the mucosal lining of the gastrointestinal tract, thereby enhancing the residence time at the absorption site and improving drug bioavailability (Vasir *et al.*, 2003). These microspheres offer several advantages, including ease of administration, uniform drug distribution, better stability, and protection of labile drugs from enzymatic degradation. The use of natural and synthetic polymers such as sodium alginate, chitosan, Carbopol 934, and hydroxypropyl methylcellulose (HPMC) in microsphere formulation has shown promising results in modulating drug release and improving mucoadhesion (Chien *et al.*, 1992; Shaji *et al.*, 2002).

Considering these factors, the present study is designed to formulate and evaluate bio-adhesive microspheres of Vildagliptin using various mucoadhesive polymers. The goal is to develop a controlled-release system that ensures prolonged gastrointestinal residence time, enhances absorption, and improves patient compliance. This approach not only aims to optimize the therapeutic efficacy of Vildagliptin but also supports the development of novel oral delivery systems for other short-acting antidiabetic agents.

MATERIALS AND METHODS

Materials

The formulation development of bio-adhesive microspheres involved the use of Vildagliptin, obtained as a gift sample from Pharmaceutical Company. Various polymers such as HPMC K4, HPMC K15, and PVP K30 were sourced from LobaChemie Pvt. Ltd., Mumbai, and served as matrix-forming and mucoadhesive agents. Analytical-grade solvents including methanol, ethanol, and chloroform were procured from Qualigens Fine Chemicals, Mumbai, and were used in the preparation and processing of the microspheres. All chemicals and reagents used were of pharmaceutical or analytical grade.

Methods

Preparation of bioadhesive microspheres of Vildagliptin

Vildagliptin-loaded bioadhesive microspheres were prepared using the ionotropic gelation method. Initially, a 1% w/v chitosan stock solution was prepared by dissolving chitosan in 5% v/v acetic acid at room temperature. Separately, 20 mg of Vildagliptin was dissolved in 5 ml of the chitosan solution to ensure uniform drug dispersion. In another preparation, a 1% sodium tripolyphosphate (TPP) solution was prepared in distilled water. The TPP solution was then added dropwise to the drug-loaded chitosan solution using a syringe under continuous magnetic stirring. This ionic interaction between chitosan and TPP facilitated the formation of microspheres. After 30 minutes of stirring, the microspheres were filtered, washed with distilled water, and air-dried for 24 hours. To ensure complete drying and stability, the microspheres were further dried in a hot air oven at 40°C for 6 hours (Sharma *et al.*, 2017).

Evaluation of mucoadhesive microspheres

Percentage Yield

The prepared microspheres (F1-F6) were collected and weighed for each formulation code (Priyadarshini *et al.*, 2014). The percentage yield (%) was calculated using formula given below:

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Entrapment Efficiency

Amount of Vildagliptin in each formulation was calculated according to procedure given below:

Equivalent to 10mg of chitosan microspheres from each batch were accurately weighed. The powder of chitosan microspheres were dissolved in 10 ml 0.1 N HCl and centrifuged at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The supernant was analyzed for drug content by measuring the absorbance at 210nm (Berthold *et al.*, 1996).

Stability of chitosan microspheres in 0.1 N HCl

The stability of chitosan microspheres in 0.1 N HCl was determined by incubating 0.5% wt/vol suspension of the microspheres in 0.1N HCl for 12 hrs. and measuring the transmission of the samples at 210nm (Labindia 3000+ spectrophotometer) as reported by Dhanaraju *et al.*, (2009). Chitosan is soluble in acidic pH, therefore, the purpose of carrying out this study was to determine the effect of different cross-linking methods on the solubility of chitosan, which in turn reflects the stability at acidic pH.

Measurement of mean particle size

The mean particle size of the microspheres was determined by Photon Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern particle size analyser**)** at a scattering angle of 90°. A sample (0.5mg) of the microsphere suspended in 5 ml of distilled water was used for the measurement (Thejeswini *et al.*, 2014).

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zetasizer (Malvern particle size analyser) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate (Dhawan *et al.*, 2004).

Flow property determination of the microspheres (Wang *et al.*, 2014)

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\textbf{LBD (Loose bulk density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\textbf{TBD (Tapped bulk density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\textbf{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X}100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\text{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

***In-vitro* drug release studies**

The prepared microspheres were evaluated for *in vitro* drug release. The drug release studies were carried out using USP I Basket type dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

A weighed quantity of formulation (equivalent to 10mg) was filled in capsule and kept in basket of dissolution apparatus with dissolution media 0.1 N HCl (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 5ml by media. The samples withdrawn were assayed spectrophotometrically at 210nm for percent of release from mucoadhesive microspheres using UV visible spectrophotometer. The release of mucoadhesive microsphere was calculated with the help of Standard curve of Vildagliptin (Lim *et al.,* 2000).

RESULTS AND DISCUSSION

The formulated Vildagliptin-loaded chitosan microspheres were evaluated for various parameters to assess their suitability as a controlled drug delivery system. The percentage yield (Table 2) ranged from 63.32% to 72.45%, with formulation F3 showing the highest yield (72.45 ± 0.36) and entrapment efficiency ($73.32 \pm 0.15\%$). This suggests that F3 had an optimal polymer-to-drug ratio, allowing for efficient drug entrapment without significant loss during processing.

Stability studies in 0.1 N HCl (Table 3) indicated that the microspheres retained their integrity over 12 hours, though there was a gradual reduction in transmittance with time, reflecting controlled release and sustained matrix stability in acidic conditions. F3 showed the slowest decrease in transmittance, supporting its better stability among the formulations.

Flow property analysis (Table 4) demonstrated that all formulations possessed good flow characteristics, as indicated by acceptable Carr's Index (below 25%) and Hausner's ratio values (below 1.35). F3 again showed favorable results (Carr's Index 22.56%, Hausner's Ratio 1.291), suggesting good compressibility and ease of handling.

In-vitro drug release studies (Table 5 and Figures 3–5) clearly differentiated the release profiles of the plain drug and the microspheres. The plain drug released over 68% within 3 hours, while the microsphere formulation (F3) released only 26.65% in the same period, and exhibited sustained release up to 96.65% over 12 hours. This controlled release behavior is attributed to the mucoadhesive and gel-forming nature of chitosan, which retards drug diffusion.

Regression analysis (Table 6) of the drug release kinetics showed that formulation F3 followed zero-order kinetics ($R^2 = 0.9981$), suggesting a constant drug release rate independent of concentration. The high correlation in the Peppas model ($R^2 = 0.996$)

also supports a diffusion-controlled release mechanism.

Formulation F3 emerged as the most promising formulation based on yield, entrapment efficiency, stability, flow properties, and sustained drug release profile, making it a suitable candidate for developing a bioadhesive microsphere system for controlled Vildagliptin delivery.

Table 1: Formulations of chitosan mucoadhesive microspheres

S. No.	Formulation Code	Vildagliptin (mg)	Chitosan (mg)	Sodium tripolyphosphate (mg)
1.	**F1**	20	100	500
2.	**F2**	20	150	500
3.	**F3**	20	200	500
4.	**F4**	20	100	750
5.	**F5**	20	150	750
6.	**F6**	20	200	750

Table 2: Percentage Yield for Different Formulation

S. No.	Formulation	Percentage Yield* (Mean ± S.D)	% Entrapment Efficiency* (Mean ± S.D)
1	F1	63.32±0.45	65.58±0.85
2	F2	65.58±0.25	70.12±0.32
3	F3	72.45±0.36	73.32±0.15
4	F4	63.32±0.35	60.25±0.60
5	F5	70.95±0.21	65.58±0.35
6	F6	67.74±0.18	64.45±0.14

***Average of three determinations (n=3)**

Table 3: Stability of Chitosan microspheres in 0.1 N HCl

S. No.	Formulation code	% Transmittance		
		2 hrs	8 hrs	12 hrs
1	F1	65.58	45.65	25.65
2	F2	69.98	43.32	18.85
3	F3	59.98	35.65	12.25
4	F4	65.58	42.25	20.32
5	F5	62.25	38.85	18.85
6	F6	68.98	45.65	22.32

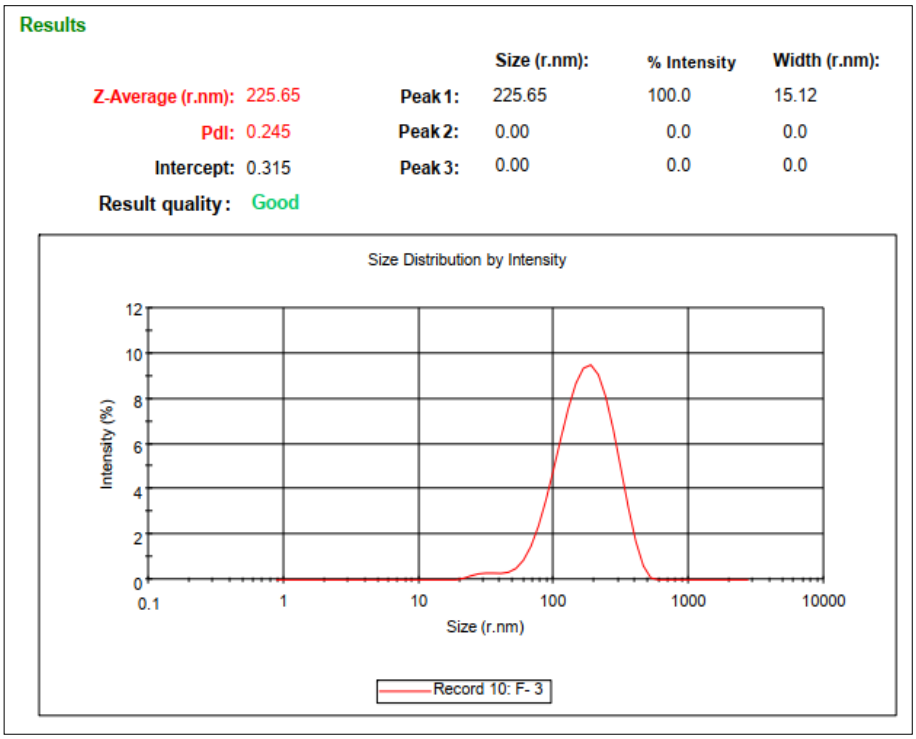

Figure 1: Particle size data of chitosan microspheres (F3)

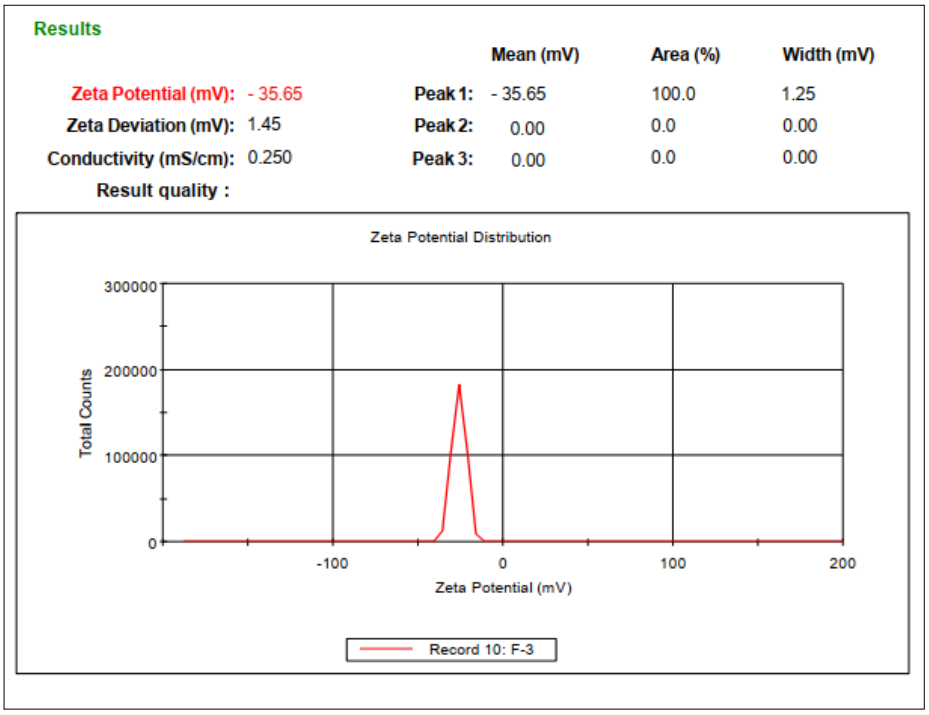

Figure 2: Zeta potential data of chitosan microspheres (F3)

Table 4: Result of Flow Properties of different microspheres formulations

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.425	0.558	23.835	1.313
F2	0.432	0.562	23.132	1.301
F3	0.412	0.532	22.556	1.291
F4	0.465	0.575	19.130	1.237
F5	0.474	0.589	19.525	1.243
F6	0.436	0.546	20.147	1.252

Table 5: Cumulative % drug release of Vildagliptin from plain drug and Chitosan microspheres

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release	
			Plain drug	Chitosan microspheres
1	SGF (pH 1.2)	1	26.65	11.25
2		2	45.65	20.23
3		3	68.85	26.65
4		4	-	38.98
5		5	-	44.65
6		6	-	56.65
7		7	-	63.32
8		8	-	73.32
9		9	-	82.32
10		10	-	90.32
11		12	-	96.65

***Simulated gastric fluid (SGF)**

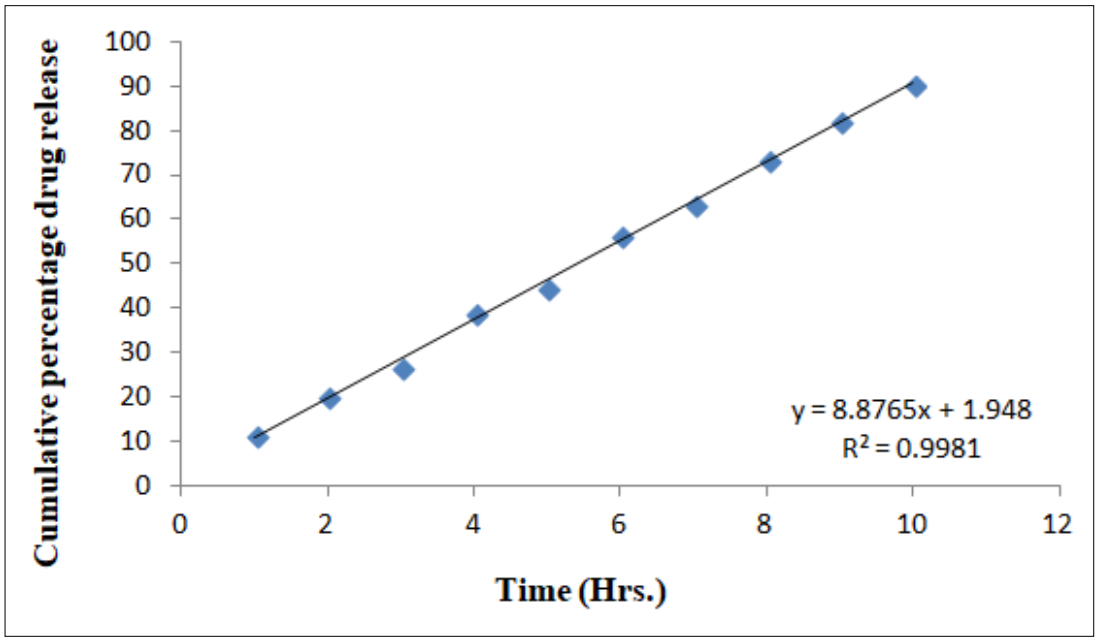

Figure 3: Cumulative Percent Drug Released Vs Time (Zero Order Plots)

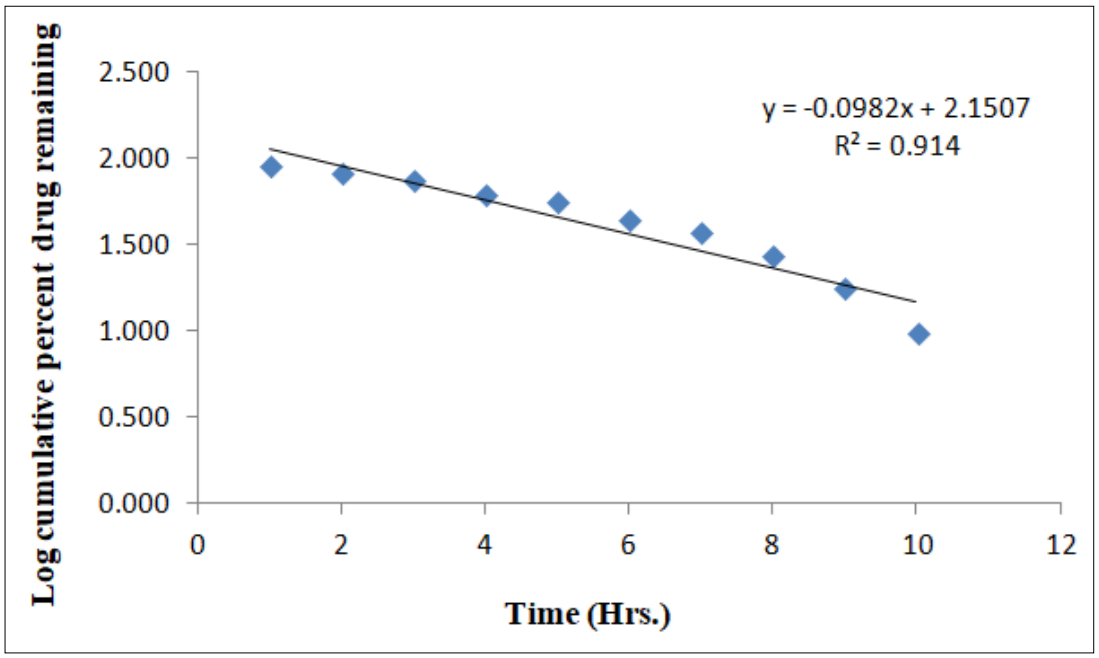

Figure 4: Log Cumulative Percent Drug Remaining Vs Time (First Order Plots)

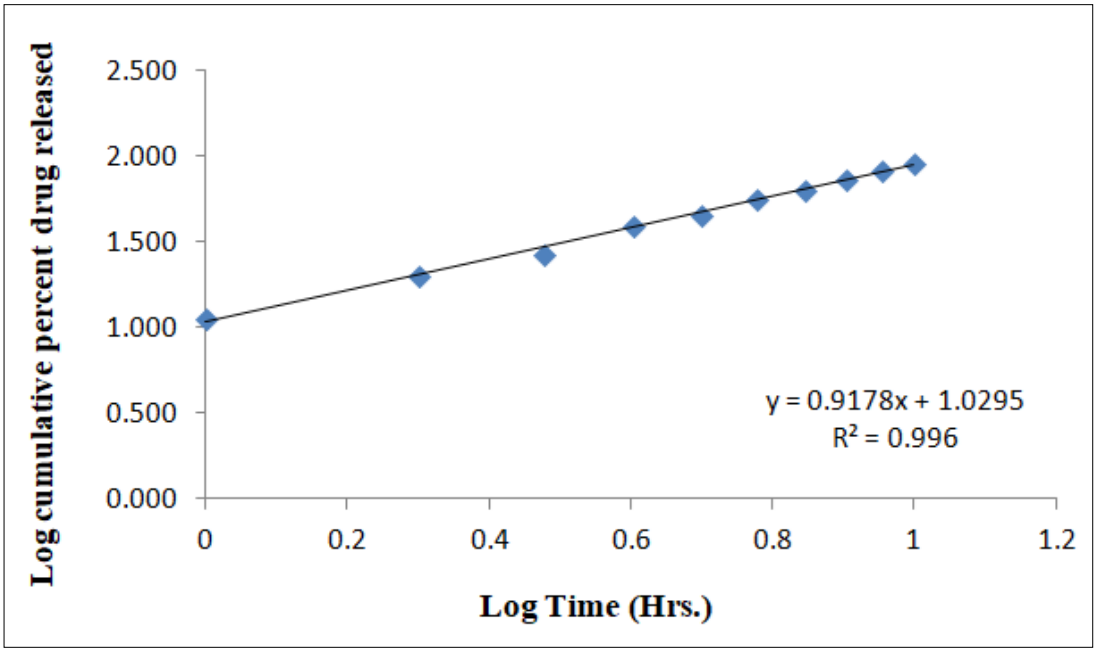

Figure 5: Log cumulative percent drug released Vs Log Time (Peppas Plots)

Table 6: Regression analysis data of microsphere formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.9981$	$R^2 = 0.914$	$R^2 = 0.996$

CONCLUSION

The present study successfully developed and evaluated bioadhesive chitosan microspheres loaded with Vildagliptin using the ionotropic gelation method. Among all the formulations, F3 exhibited optimal characteristics with the highest percentage yield and entrapment efficiency. The microspheres demonstrated good flow properties, indicating ease of processing and handling. In vitro drug release studies confirmed that the chitosan microspheres significantly prolonged the release of Vildagliptin compared to the plain drug, achieving nearly complete release over 12 hours. Kinetic modeling suggested that the drug release followed zero-order kinetics with a diffusion-controlled mechanism. The results strongly indicate that chitosan-based microspheres are a promising platform for the sustained and controlled delivery of Vildagliptin, potentially improving therapeutic efficacy and patient compliance in the management of diabetes.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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