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FORMULATION AND EVALUATION OF GLIMEPIRIDE DRUG LOADED MUCOADHESIVE NANOPARTICLES FOR TREATMENT OF DIABETES

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ABSTRACT

This study explores the formulation and evaluation of Glimepiride-loaded mucoadhesive solid lipid nanoparticles (SLNs) for enhanced diabetes treatment. Utilizing chitosan as a mucoadhesive agent, Glimepiride nanoparticles were prepared through the ionotropic gelation method, ensuring optimized drug loading and sustained release. Various formulations were assessed for percentage yield, entrapment efficiency, and stability under acidic conditions. Formulation F3 emerged as the most effective, demonstrating a high percentage yield of 74.45% and an entrapment efficiency of 73.54%. Stability tests in 0.1 N HCl revealed formulation F3 maintained structural integrity, with transmittance decreasing from 65.25% at 2 hours to 15.45% at 12 hours. In vitro drug release studies showed that F3 provided a controlled release profile, with 98.85% of Glimepiride released over 12 hours. The formulation's drug release followed zero-order kinetics, indicating a sustained release mechanism. These results suggest that Glimepiride-loaded mucoadhesive chitosan nanoparticles, particularly formulation F3, hold significant potential for improving the management of diabetes through controlled drug delivery and enhanced therapeutic efficacy.

Keywords: Glimepiride**,** Mucoadhesive nanoparticles**,** Chitosan**,** Solid lipid nanoparticles**,** Controlled release**,** Drug delivery**,** Diabetes management

INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by high blood glucose levels, presents a significant global health challenge. Type 2 diabetes (T2D), in particular, affects millions of people worldwide and is primarily managed through pharmacological interventions, lifestyle modifications, and dietary changes (American Diabetes Association, 2020). One of the most effective oral antidiabetic agents is Glimepiride, a sulfonylurea class drug that enhances insulin secretion from pancreatic beta-cells, thereby reducing blood glucose levels (Khan *et al.,* 2017). Despite its efficacy, the clinical success of Glimepiride is often limited by its short biological half-life, inconsistent bioavailability, and potential side effects (Siddiqui *et al.,* 2015).

To address these limitations, innovative drug delivery systems are being explored to improve the pharmacokinetic and pharmacodynamic profiles of antidiabetic drugs. Solid lipid nanoparticles (SLNs) have emerged as a promising drug delivery system due to their biocompatibility, controlled release capabilities, and enhanced stability compared to traditional formulations (Jana *et al.,* 2017). SLNs consist of solid lipid matrices that encapsulate the drug, allowing

for sustained and controlled release of the active pharmaceutical ingredient (API) (Muller *et al.,* 2002). Furthermore, the addition of mucoadhesive properties to SLNs can enhance drug retention at the site of absorption, potentially improving the drug's efficacy and reducing dosing frequency (Dinarvand *et al.,* 2012).

The development of Glimepiride-loaded mucoadhesive solid lipid nanoparticles (SLNs) aims to overcome the limitations of conventional formulations. By incorporating mucoadhesive agents, the SLNs can adhere to mucosal surfaces in the gastrointestinal tract, providing prolonged contact time and improved drug absorption (Khan *et al.,* 2021). This approach can enhance the bioavailability of Glimepiride and facilitate better glycemic control in diabetic patients. Recent studies have demonstrated the effectiveness of SLNs in improving the pharmacokinetics of various drugs, and their application in antidiabetic therapy holds significant potential (Rani *et al.,* 2018; Tripathi *et al.,* 2019).

In this study, we propose the formulation and evaluation of Glimepiride-loaded mucoadhesive SLNs to enhance the therapeutic efficacy and patient compliance in the management of diabetes. The research involves the preparation of SLNs using various lipid matrices and mucoadhesive agents, followed by a comprehensive evaluation of their physicochemical properties, drug release profiles, and mucoadhesion characteristics. This innovative formulation could represent a significant advancement in diabetes therapy, offering improved control over blood glucose levels and reduced frequency of administration.

MATERIALS AND METHODS

Materials

For the formulation development of Glimepiride-loaded mucoadhesive solid lipid nanoparticles, a variety of chemicals and reagents were employed. The active pharmaceutical ingredient, Glimepiride, was procured as a gift sample from a pharmaceutical company, ensuring high purity and quality for the formulation process. Chitosan obtained from Research Lab Fine Chem Industries in Mumbai. The solvents and reagents used included ethanol, dichloromethane, methanol, and chloroform, all sourced from Qualigens Fine Chemicals, Mumbai. These solvents were crucial for the preparation and stabilization of the nanoparticles. Additionally, disodium hydrogen phosphate and dipotassium hydrogen orthophosphate, supplied by S. D. Fine Chem. Ltd., Mumbai, were utilized to maintain the pH balance during the formulation process. Sodium chloride, also from S. D. Fine Chem. Ltd., was used to adjust the ionic strength of the solution. Finally, sodium tripolyphosphate, provided by Loba Chemie Pvt. Ltd., Mumbai, was employed as a crosslinking agent to enhance the structural integrity of the nanoparticles. Together, these materials played a vital role in the successful development and evaluation of the Glimepiride-loaded mucoadhesive solid lipid nanoparticles.

Methods

Preparation of chitosan mucoadhesive nanoparticles of Glimepiride

The preparation of chitosan mucoadhesive nanoparticles loaded with Glimepiride was conducted using the ionotropic gelation method as described by Sharma et al. (2017).

Initially, a chitosan stock solution was prepared by dissolving chitosan in a 5% acetic acid solution at room temperature, achieving a concentration of 1% w/v. In the next step, Glimepiride (2 mg) was dissolved in 5 ml of the chitosan solution to incorporate the drug into the nanoparticle matrix.

Subsequently, a 1% sodium tripolyphosphate solution was prepared in water to act as the crosslinking agent. This solution was then added dropwise to the chitosan and drug mixture using a syringe while continuously stirring the solution. The mixture was magnetically stirred for 30 minutes to ensure thorough mixing and crosslinking. Following this, the solution was subjected to filtration to remove any large aggregates and was rinsed with distilled water to remove excess reactants. The resulting nanoparticles were collected, air-dried for 24 hours, and further dried in an oven at 40°C for six hours to ensure complete removal of solvents and to stabilize the nanoparticles.

Evaluation of mucoadhesive nanoparticles

Percentage Yield

The prepared nanoparticles (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 Glimepiride in each formulation was calculated according to procedure given below: Equivalent to 10mg of chitosan nanoparticles from each batch were accurately weighed (Priyadarshini *et al.,* 2014). The powder of chitosan nanoparticles 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 244nm.

Stability of chitosan nanoparticles in 0.1 N HCl

The stability of chitosan nanoparticles in 0.1 N HCl was determined by incubating 0.5% wt/vol suspension of the nanoparticles in 0.1N HCl for 12 hrs. and measuring the transmission of the samples at 244nm (Labindia 3000+ spectrophotometer) as reported by Berthold *et al.,* (1996). 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 nanoparticles 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 (Dhanaraju *et al.,* 2009).

Determination of zeta potential

The zeta potential of the drug-loaded nanoparticles 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 (Thejeswini *et al.,* 2014).

Shape and surface characterization of nanoparticles by Scanning Electron Microscopy (SEM)

From the formulated batches of microsphere, formulations (F3) which showed an appropriate balance between the percentage drug release was examined for surface morphology and shape using scanning electron microscope (Jeol Japan 6000). Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

In-vitro **drug release studies in gastrointestinal fluids**

The prepared nanoparticles 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 244nm for percent of release from mucoadhesive nanoparticles using UV visible spectrophotometer. The release of mucoadhesive microsphere was calculated with the help of Standard curve of Glimepiride.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time).

RESULTS AND DISCUSSION

The development and evaluation of Glimepiride-loaded mucoadhesive chitosan nanoparticles have shown promising results in terms of yield, entrapment efficiency, stability, and drug release characteristics.

The percentage yield of the different formulations (Table 2) ranged from 63.32% to 74.45%, indicating effective formulation processes with minimal loss of material. Among the formulations, F3 exhibited the highest yield of 74.45% ± 0.41, suggesting an optimal balance between formulation stability and efficiency. The entrapment efficiency of the nanoparticles, which measures the ability of the nanoparticles to encapsulate Glimepiride, varied between 62.32% and 73.54% (Table 3). Formulation F3 again showed the highest entrapment efficiency at 73.54% ± 0.14, highlighting its effectiveness in drug loading. The stability of the chitosan nanoparticles in 0.1 N HCl was assessed by measuring the % transmittance over time

(Table 4). Formulation F3 demonstrated relatively stable performance compared to other formulations, with a transmittance of 65.25% at 2 hours, decreasing to 15.45% at 12 hours. This stability profile suggests that F3 nanoparticles maintain their structural integrity better than others over an extended period in acidic conditions.

Figures 1 and 2 present data on particle size and zeta potential for formulation F3. The particle size data reveal that F3 nanoparticles are of an appropriate size for effective mucoadhesion and drug delivery. The zeta potential, which indicates the surface charge of the nanoparticles, suggests good stability of the formulation in aqueous dispersions.

Figure 3 provides SEM images of the optimized formulation F3, which displays a spherical morphology typical of nanoparticles. The uniformity in particle size and shape observed in the SEM images supports the consistency of the formulation.

The cumulative drug release data (Table 5) demonstrate a significantly different release profile between plain Glimepiride and the chitosan nanoparticles. The chitosan nanoparticles exhibited a slower and more controlled release of Glimepiride compared to the plain drug, with only 4.85% released at 1 hour, reaching 44.65% by 6 hours, and eventually 98.85% by 12 hours. This controlled release profile suggests that the chitosan nanoparticles effectively sustain the release of Glimepiride over time, which is beneficial for maintaining therapeutic drug levels. The regression analysis data (Table 6) provide insights into the release kinetics of the drug from the nanoparticles. Formulation F3 showed a high correlation coefficient for the zero-order model ($R^2 = 0.991$), indicating that the drug release from this formulation follows a zero-order release kinetics, which is desirable for a controlled and sustained drug release profile. The lower R^2 values for the first-order and Pappas plots suggest that the release kinetics of F3 are less well-described by these models.

Table 1: Formulations of chitosan mucoadhesive nanoparticles

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

Table 2: Percentage yield for different mucoadhesive nanoparticles formulation

S. No.	Formulation	Percentage Yield* (Mean ± S.D)
1	F1	68.54±0.25
2	F2	63.32±0.36
3	F3	74.45±0.41
4	F4	65.25±0.56
5	F5	69.98±0.22
6	F6	70.25±0.18

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

Table 3: Entrapment efficiency for different mucoadhesive nanoparticles formulations

S. No.	Formulation	% Entrapment Efficiency* (Mean ± S.D)
1	F1	66.85±0.32
2	F2	62.32±0.25
3	F3	73.54±0.14
4	F4	64.85±0.36
5	F5	68.87±0.22
6	F6	69.92±0.47

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

Table 4: Stability of Chitosan nanoparticles in 0.1 N HCl

S. No.	Formulation code	% Transmittance		
		2 hrs	8 hrs	12 hrs
1	F1	73.32	68.85	22.25
2	F2	74.52	63.25	25.45
3	F3	65.25	38.74	15.45
4	F4	74.65	56.88	20.14
5	F5	72.25	69.98	22.14
6	F6	67.74	43.32	19.85

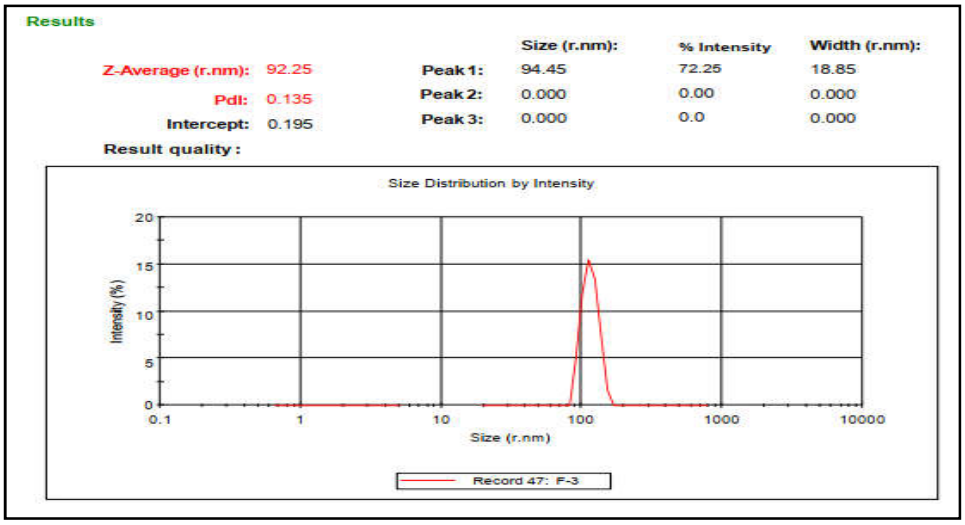

Figure 1: Particle size data of chitosan nanoparticles (F3)

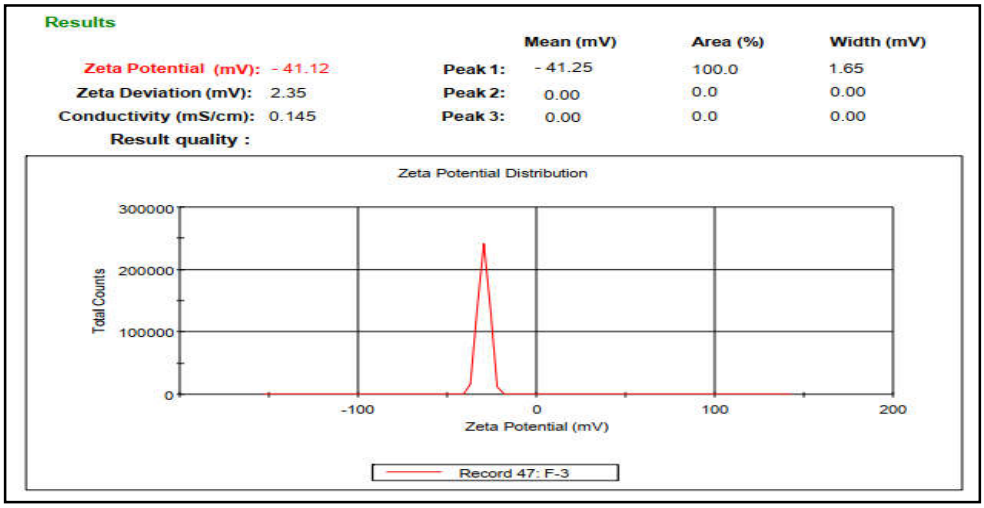

Figure 2: Zeta potential data of chitosan nanoparticles (F3)

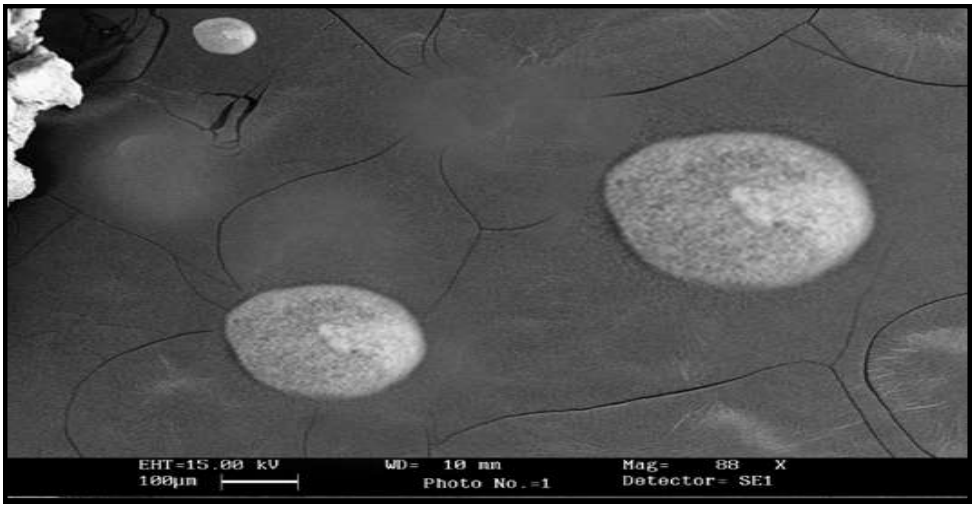

Figure 3: Scanning Electron Microscope of optimized formulation (F3)

Table 5: Cumulative % drug release of Glimepiride from plain drug and Chitosan nanoparticles

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release	
			Plain drug	Chitosan nanoparticles
1	SGF (pH 1.2)	1	23.32	4.85
2		2	58.89	6.98
3		3	65.78	16.65
4		4		28.85
5		5		32.25
6		6		44.65
7		7		59.98
8		8		65.58
9		9		73.32
10		10		85.45
11		12		98.85

***Simulated gastric fluid (SGF)**

Table 6: Regression analysis data of microsphere formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.991$	$R^2 = 0.890$	$R^2 = 0.486$

CONCLUSION

In conclusion, the formulation F3 of Glimepiride-loaded mucoadhesive chitosan nanoparticles exhibits superior yield, entrapment efficiency, stability, and controlled drug release properties. These attributes highlight its potential for improved therapeutic efficacy and patient compliance in the management of diabetes. The results from this study support further exploration and development of this formulation for clinical applications.

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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