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Fabrication Of Glimepiride-Loaded Nanospongesby Emulsion Solvent Evaporation Method

Jyoti Gupta[1], Poonam Maurya[1]*, Raj Keshwar Prasad[1], Shaima K A[1]

[1]*Shambhunath Institute of Pharmacy, Prayagraj, U.P., India 211015

***Corresponding Author:** Poonam Maurya
*Email: poonammaurya66@gmail.com

ABSTRACT
Diabetes mellitus, particularly type 2 diabetes mellitus, is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to elevated blood glucose levels, which, if unmanaged, can cause serious complications like cardiovascular diseases, neuropathy, and kidney failure. The present study focuses on the development and evaluation of Glimepiride-loaded nanosponges using ethyl cellulose as a polymer through the emulsion solvent evaporation methodenhanced by ultrasonic assistance. Glimepiride, an oral hypoglycemic agent used for type 2 diabetes mellitus, is commonly prescribed to help regulate blood glucose levels by stimulating insulin secretion from the pancreas. However, its clinical effectiveness is often limited due to its poor water solubility and low bioavailability, resulting in suboptimal glycemic control. To address Glimepiride's limitations, nanosponges were synthesized using dichloromethane as a solvent and polyvinyl alcohol as a stabilizer. The nanosponges were characterized by particle size analysis, zeta potential, scanning electron microscopy, entrapment efficiency, product yield, and Fourier-transform infrared spectroscopy. The results showed that the nanosponges had a nanoscale size (291 to 412 nm), good stability (polydispersity index: 0.282to 0.527; and zeta potential: -16.8 to -29.3 mV.), and a porous structure, with Glimepiride successfully encapsulated (entrapment efficiency: 86.4±1.7 to 97.4±1.1) in the polymer matrix. FT-IR analysis indicated no interaction between the drug and excipients. *In-vitro* drug release studies indicated a sustained release profile over 12 hours. The findings suggest that Glimepiride-loaded nanosponges can significantly improve solubility, stability, and controlled drug release, offering a potential solution for enhancing the therapeutic efficacy of Glimepiride in the long-term management of diabetes mellitus.

Keywords: Glimepiride, Nanosponges, Bioavailability enhancement, Diabetes Mellitus, Ethyl Cellulose, Emulsion solvent evaporation method etc.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a widespread chronic metabolic disorder characterized by insulin resistance and an inability to regulate blood glucose levels effectively. The incidence of diabetes is increasing globally, with T2DM accounting for the majority of cases. Prolonged high blood sugar levels can lead to severe complications, such as cardiovascular disease, nerve damage, and kidney dysfunction, making effective management of blood glucose levels crucial. Glimepiride (Figure 1), is an oral antidiabetic agent belonging to the sulfonylurea class, often prescribed for T2DM due to its ability to enhance insulin secretion from pancreatic beta cells. Glimepiride (Glm) interacts with specific receptors on pancreatic β cells, resulting in the closure of potassium channels. This causes depolarization of the cell membrane and subsequent opening of calcium channels. The secretion of insulin is subsequently initiated by the inflow of calcium. However, its therapeutic efficacy is hindered by poor water solubility and limited bioavailability, necessitating frequent dosing and leading to inconsistent blood glucose control [1].

To address these issues, advanced drug delivery systems like nanosponges have been explored. Nanosponges are porous nanoparticles that can enhance drug solubility, and stability, and provide sustained release, making them promising carriers for improving drug delivery. These systems not only improve drug solubility and stability but also allow for sustained and targeted drug release, potentially enhancing therapeutic outcomes while reducing side effects. The word "Nanosponges" refers to porous-structured nanoparticles. Nanosponges are little sponges-like particles featuring cavities that measure only a few nanometres in width (Figure 2). They can transport hydrophilic and lipophilic compounds and enhance the solubility of poorly water-soluble molecules. Despite their solubility in water, they do not undergo chemical disintegration within it. They possess the capability to convert liquid substances into solids, mask undesirable flavours, and serve as a transport medium [2, 3].

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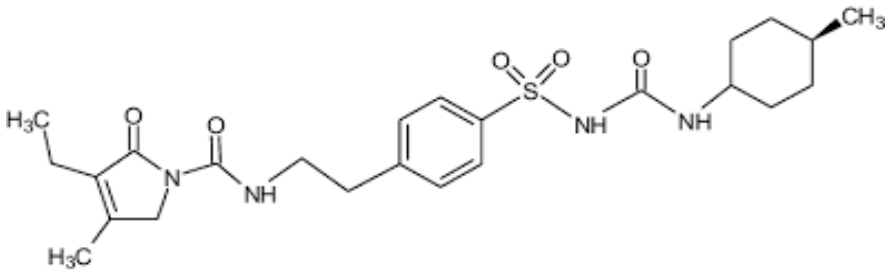

Figure 1: Chemical Structure of Glimepiride

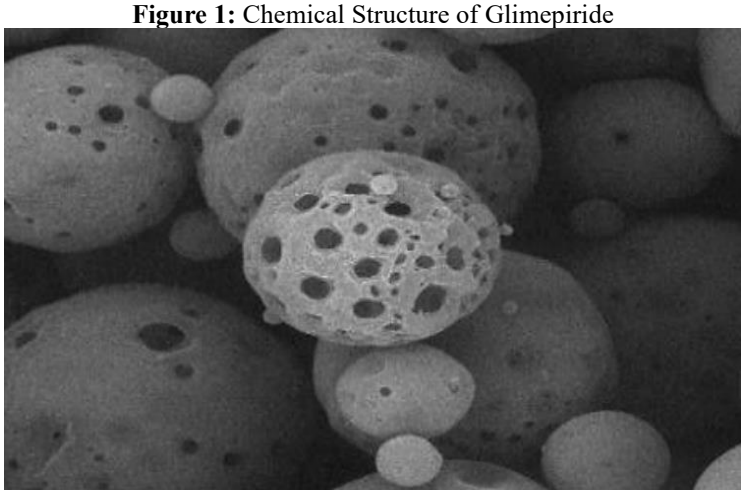

Figure 2: Nanosponges

Nanosponges can be prepared in several dosage forms for oral, parenteral, topical, or inhalation. They are put into certain dosage forms and move throughout the body until they reach the intended target location. After binding to the surface, they begin to release the medication in a predictable and controlled manner [4 5].

One of the hardest things in drug research is still trying to make poorly soluble and virtually insoluble substances more soluble and soluble. Numerous techniques have been developed to speed up how these medications dissolve, absorb orally, and boost their bioavailability. Nanosponges have demonstrated encouraging results in increasing solubility, wettability, dissolving rate, and bioavailability [6,7].

There are several types of Nanosponges formed based on different polymers and materials (Figure 3).

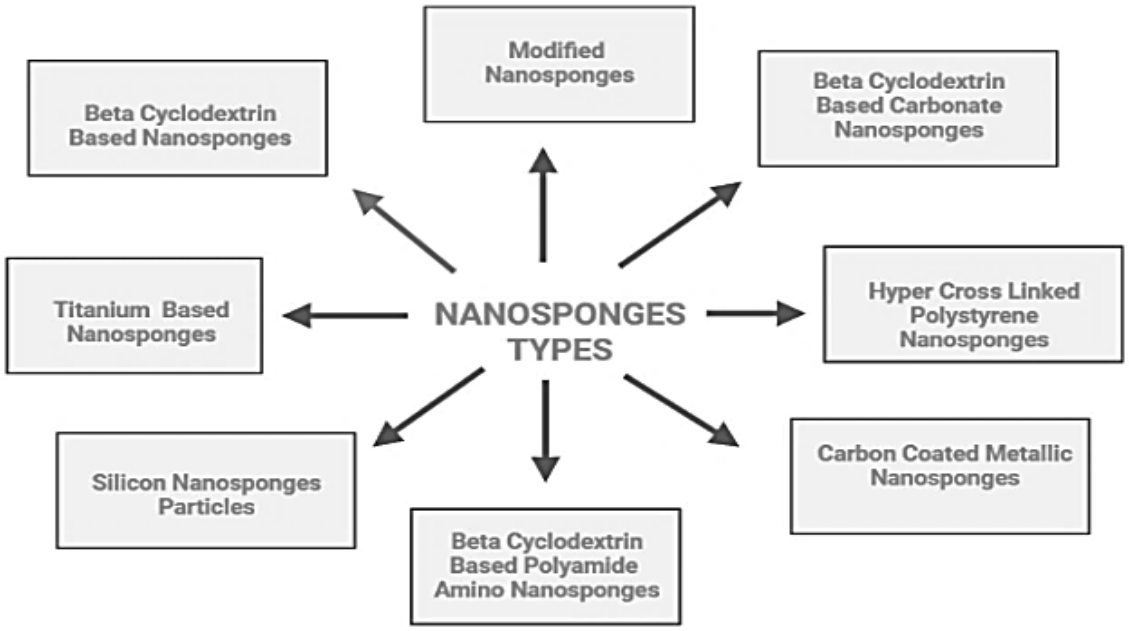

Figure 3: Types of Nanosponges

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1S (2024)
http://www.veterinaria.org
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Commonly, nanosponges are made up of cross-linked cyclodextrins and organic carbonates. The following three elements make up the majority of nanosponges. These elements are the Polymer, Cross-linking agent, and the Drug substance (Figure 4).

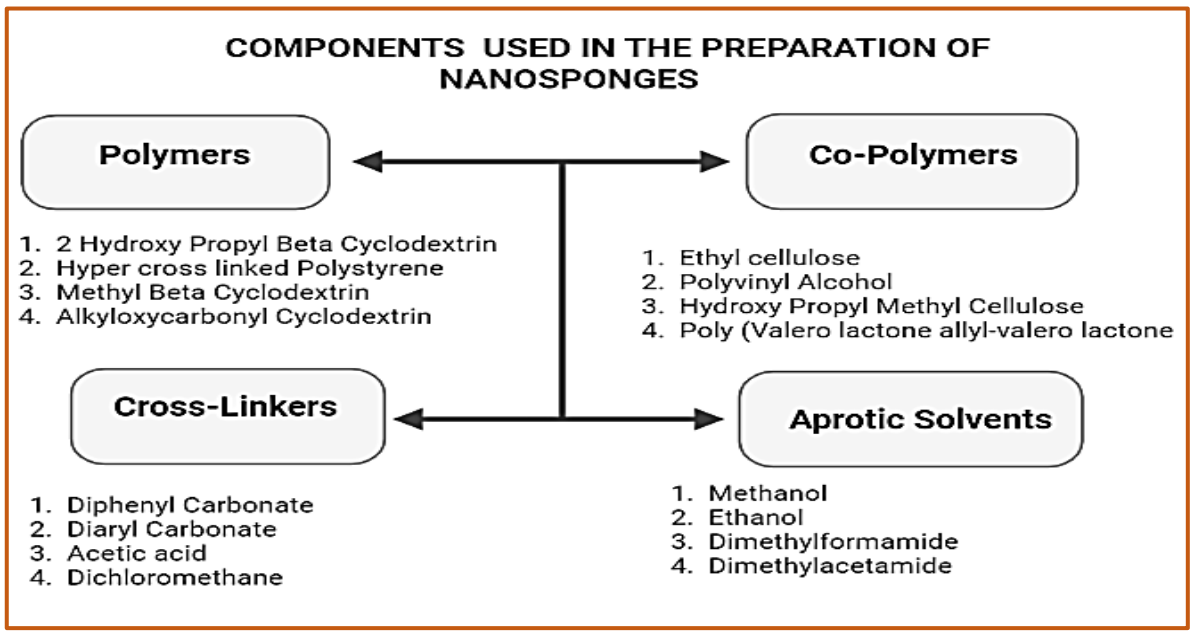

Figure4: Component used in Nanosponges Preparation

Ethyl cellulose, a biocompatible and widely used polymer, offers an excellent matrix for developing nanocarriers due to its ability to provide controlled and sustained drug release.
This study focuses on the development of Glimepiride-loaded Nanosponges (GNS) using ethyl cellulose as the polymer matrix, utilizing the emulsion solvent evaporation method with ultrasonic assistance. Dichloromethane was used as the solvent, and polyvinyl alcohol (PVA) served as the stabilizer. The nanosponges were characterized by particle size analysis, morphology, zeta potential measurement, drug entrapment efficiency (% EE), product yield, Fourier-transform infrared (FT-IR) spectroscopy, and *in-vitro* drug release. The objective of this study is to improve the solubility, stability, and controlled release of Glimepiride, enhancing its effectiveness in the long-term management of T2DM. This investigation contributes to advancements in nanotechnology-based drug delivery systems, exploring the potential of nanosponges as a solution for optimizing antidiabetic drug therapy.

2. MATERIAL AND METHODS

2.1 Materials Used

Glimepiride was acquired from Jubilant Life Sciences in Uttar Pradesh, India. We bought Ethyl cellulose from S.D. Fine Ltd. in India. While Dichloromethane was acquired from Falcon Chemicals India, HPLC grade Methanol was acquired from Loba Chem Private Ltd., India. The source of the Polyvinyl alcohol and Ethanol was Thomas Baker Chemicals Pvt. Ltd. located in Mumbai, India. All the chemicals utilized were of analytical grade.

2.2 Methods

2.2.1 Formulation of Glm Nanosponges

Glimepiride (Glm) loaded nanosponges were generated utilizing an emulsion solvent evaporation approach with ultrasonication assistance. For this purpose, Glm was dissolved in an Ethyl cellulose (EC) solution (in Dichloromethane (DCM)) using sonication for one minute. After that, the produced drug solution was emulsified drop by drop into 100 milliliters of aqueous phase (100 milliliters), including a variable amount of PVA (Polyvinyl alcohol) under probe sonication with magnetic stirring at 1000 rpm. The formed emulsion was swirled at 1000 rpm for approximately 24 hours at room temperature under a magnetic stirrer. The prepared Glm nanosponges were collected by ultracentrifugation for one hour at 15000 rpm, then lyophilization for the whole night. Following collection, the nanosponges were used for further characterization and placed in a well-sealed vial [8].

2.2.2 Formulation Optimization

Different formulas were generated by varying the concentration of Ethyl Cellulose, PVA%, and stirring speed of the magnetic stirrer. Table 1 shows the various formulas generated for the development of Glm nanosponges.

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1S (2024)
http://www.veterinaria.org
Article Received: Revised: Accepted:

Table 1: Formula for Development of Glimepiride Nanosponges

S.No.	Formula Code	Glimepiride (mg)	Ethyl Cellulose (mg)	DCM (ml)	PVA% (mg)	PVA (ml)	RPM
1	GNS 1	5	100	10	0.5	25	1100
2	GNS 2	5	500	10	1.75	25	1500
3	GNS 3	5	300	10	1.75	25	1100
4	GNS 4	5	300	10	1.75	25	1100
5	GNS 5	5	100	10	1.75	25	700
6	GNS 6	5	500	10	0.5	25	1100
7	GNS 7	5	500	10	1.75	25	700
8	GNS 8	5	300	10	1.75	25	1100
9	GNS 9	5	500	10	3	25	1100
10	GNS 10	5	100	10	3	25	1100
11	GNS 11	5	300	10	0.5	25	700
12	GNS 12	5	300	10	1.75	25	1100
13	GNS 13	5	300	10	1.75	25	1100
14	GNS 14	5	300	10	0.5	25	1500
15	GNS 15	5	300	10	3	25	1500
16	GNS 16	5	300	10	3	25	700
17	GNS 17	5	100	10	1.75	25	1500

2.2.3 Characterization of Prepared Glm Nanosponges

The prepared Glm-loaded nanosponges were characterized for properties such as entrapment efficiency, particle size, zeta potential, polydispersity index, FTIR, SEM, and %yield.

Production Yield Determination

The following equation was used to predict the production yield of nanosponges (NS) once the initial weight of the raw materials and the final weight of the developed nanosponges have been precisely determined (Equation 1) [10].

$$Production\ Yield = \frac{Practical\ mass\ of\ Nanosponges}{Theoretical\ mass\ of\ Polymer+Drug} \times 100 \quad (1)$$

Particle Size and Particle Size Distribution Analysis

Particle size and Polydispersity Index (PDI) can be estimated by laser light diffractometry using a Malvern Zetasizer (#Nano ZS 4800, UK) at 25ºC under the scattering angle of 90º [11].

Zeta Potential Determination

Zeta potential measurements were carried out at 25°C utilizing dynamic light scattering studies using a Malvern Zetasizer apparatus (#Nano ZS 4800, UK) at a fixed scattering angle of 173°. After completing each measurement three times, an average value was determined [12].

Entrapment Efficiency Determination

The 10 ml of prepared nanosponges were ultracentrifuged at 15,000 rpm for 60 minutes at 4ºC. Following centrifugation, the amount of free drug in the supernatant was determined using UV double-beam spectrophotometer at 228 nm [13]. The % entrapment efficiency (% EE) of prepared NS was determined by using the formula (equation 2):

$$\%\ EE = \frac{Amount\ of\ Total\ Drug\ content - Amount\ of\ Free\ Drug}{Amount\ of\ Total\ Drug\ content} \times 100 \quad (2)$$

Morphological Imaging of Glm Nanosponges

The produced nanosponges' morphologies were examined under scanning electron microscopy. Based on the particle size and EE% values, the optimal formula was analyzed using a scanning electron microscope. After reconstituting with deionized water, the nanosponges samples were laid out on carbon tape. Subsequently, the samples underwent vacuum drying, gold coating, and electron microscopy examination to determine surface morphology [14].

FTIR Interaction Study

To confirm the likelihood of drug-polymer chemical bond interaction, the Fourier transform infrared spectroscopic study was conducted [15].

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http://www.veterinaria.org
Article Received: Revised: Accepted:

***In-Vitro* Drug Release Study**

The *in-vitro* drug release of several Glm nanosponges formulations over a dialysis membrane was studied, and graphs were subsequently created between cumulative percentage drug release versus time. *In-vitro* release study of pure Glm suspension was also studied. Release data was then put into various release models and the release pattern was determined.

Storage stability evaluation of Glm Nanosponges

The optimized Glm nanosponges were stored in glass bottles with plastic plugs at 4±1 °C, 25±1 °C, and 45±1 °C under 75% RH in a stability chamber for three months and evaluated for physicochemical stability of Glm nanosponges. The physicochemical stability was evaluated in terms of physical appearance, particle size, % Glm content, and % EE. The estimation was carried out in triplicate at each storage condition. The stability constant (K) and self-life were determined.

3 RESULTS AND DISCUSSION

3.1 Production Yield

To assess the effectiveness of the production procedure, the yield percentage of the generated nanosponges was computed. Based on the initial amounts of formulation ingredients employed in the production, the theoretical yield was calculated. The % production yield calculated is mentioned below in Table 2.

Table 2: Practical and % Production Yield of Glimepiride Nanosponges

S.No.	Formulation	Theoretical Yield(mg)	Practical Yield(mg)	% Production Yield
1	GNS 1	128	93	72.6
2	GNS 2	517	471	91.1
3	GNS 3	311	247	79.4
4	GNS 4	336	303	90.1
5	GNS 5	109	82	75.2
6	GNS 6	519	482	92.8
7	GNS 7	509	468	91.9
8	GNS 8	321	259	80.6
9	GNS 9	514	461	89.6
10	GNS 10	117	91	77.7
11	GNS 11	329	283	86
12	GNS 12	342	301	88
13	GNS 13	307	247	80.4
14	GNS 14	313	278	88.8
15	GNS 15	334	303	90.7
16	GNS 16	323	282	87.3
17	GNS 17	122	103	84.4

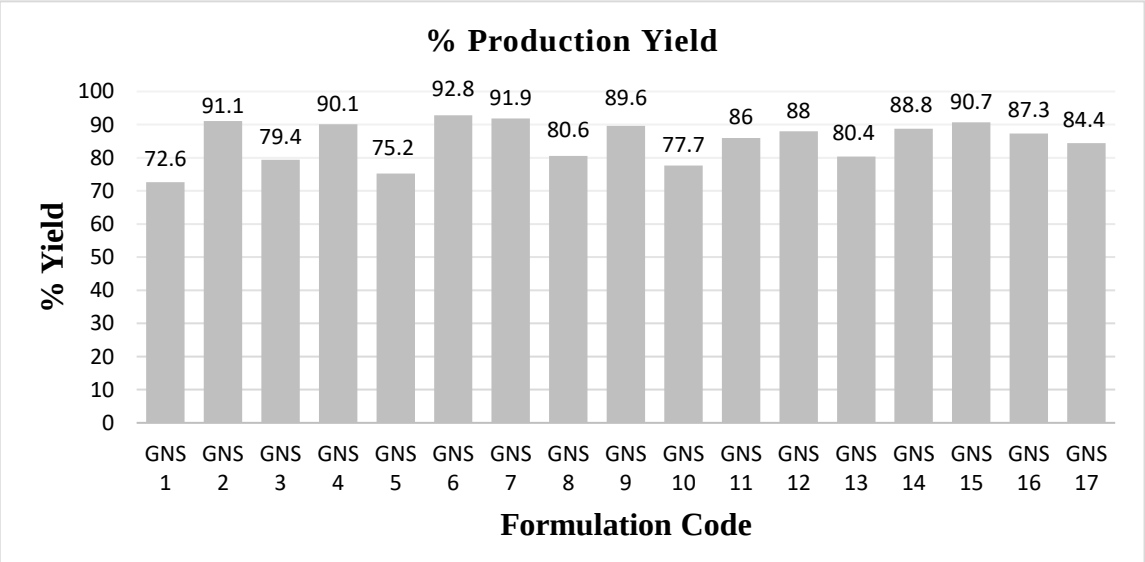

Figure 5: % Production Yield of prepared Glm Nanosponges

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1S (2024)
http://www.veterinaria.org
Article Received: Revised: Accepted:

3.2 Particle size and PDI

The prepared nanosponges' particle size was ascertained by the application of certain techniques, such as dynamic light scattering (DLS). The results of the particle size analysis are shown in Table 3. The prepared nanosponges had a polydispersity index (PDI) of between range 0.339 to 0.527 and a particle size range between 291 to 412nm. The smallest particle size was 298.4nm and the largest size was 411.5nm. The limited spread of particle sizes suggests that the size of the particles is homogeneous. This implies that homogenous nanosponges structures were produced by a consistent fabrication procedure.

Table 3: The particle size, Zeta potential, and Polydispersity index of Prepared Glm Nanosponges

S.No.	Formulation code	Particle Size (nm)	Zeta Potential (mV)	PDI
1	GNS 1	371.4±1.3	-22.3±0.8	0.463
2	GNS 2	321.6±0.9	-19.5±0.3	0.521
3	GNS 3	411.5±1.5	-28.2±0.2	0.376
4	GNS 4	381.2±1.7	-16.8±0.5	0.448
5	GNS 5	298.4±1.2	-21.6±0.4	0.428
6	GNS 6	338±1.1	-26.7±0.3	0.521
7	GNS 7	291.4±0.5	-23.9±0.2	0.282
8	GNS 8	401.6±1.6	-17.5±0.6	0.339
9	GNS 9	312.2±2.1	-22.5±0.5	0.401
10	GNS 10	372.9±0.8	-27.7±0.9	0.523
11	GNS 11	301.3±1.1	-25.3±0.4	0.388
12	GNS 12	411.1±0.4	-18.7±0.8	0.527
13	GNS 13	349.2±1.3	-25.5±0.5	0.447
14	GNS 14	308.7±2.4	-28.4±0.3	0.421
15	GNS 15	382.2±1.6	-29.1±0.2	0.362
16	GNS 16	319.2±2.5	-23.6±0.7	0.422
17	GNS 17	343.1±0.3	-20.7±0.3	0.531

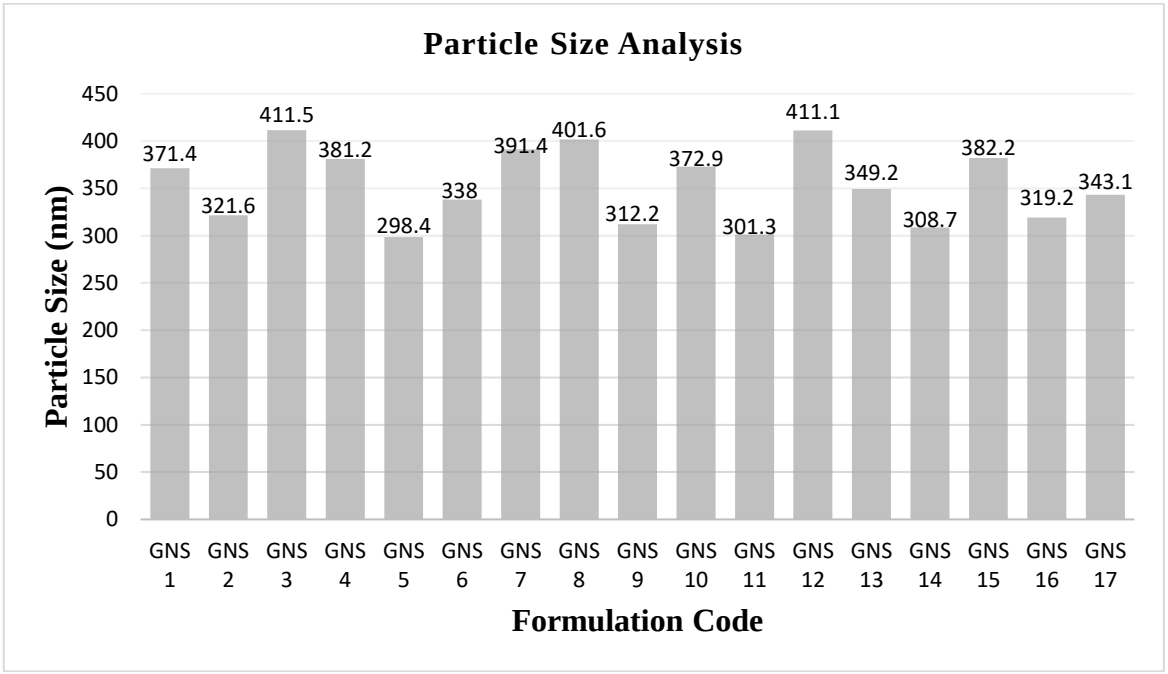

Figure 6: Particle size analysis of Glimepiride nanosponges

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
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http://www.veterinaria.org
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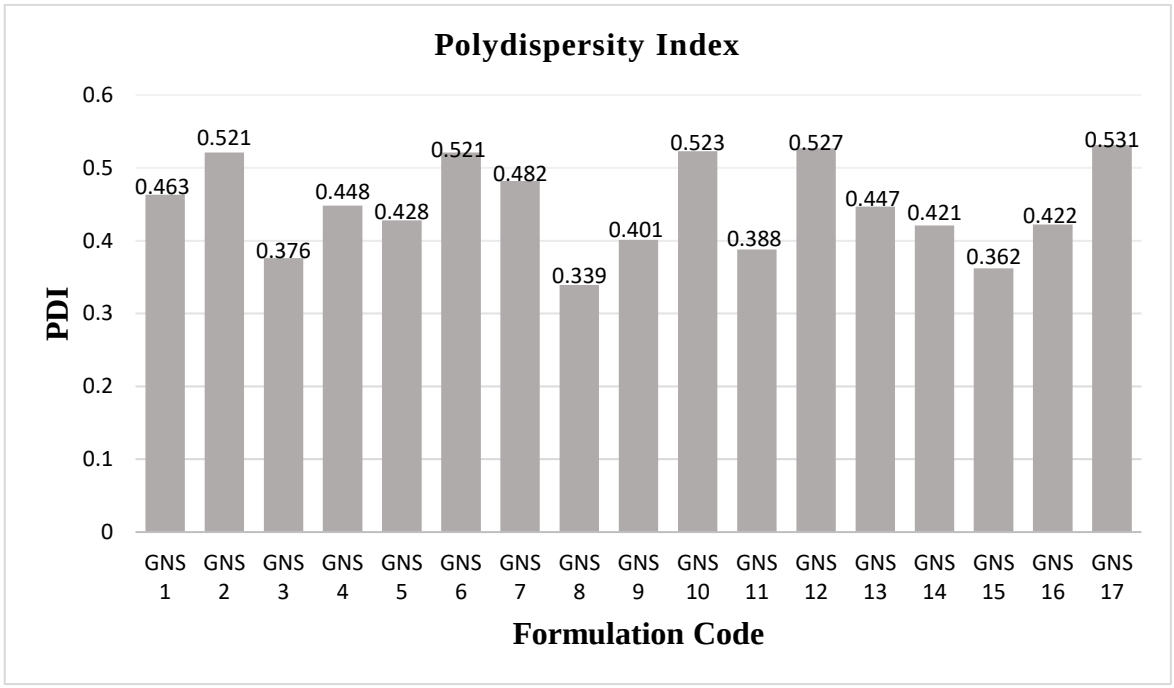

Figure 7: PDI of Prepared Glimepiride Nanosponges

The nanosponges' size plays a critical role in their capacity to encapsulate drugs, penetrate biological barriers, and remain stable in a variety of conditions. Given that the measured particle size is within the ideal range for drug delivery, they may be useful in treating diabetes mellitus.

3.3 Zeta potential

Table 3 displays the range of -16.8 to -29.3 mV for the Zeta potential of the prepared Glimepiride Nano sponges, (Figure 8 & 9). This research confirms that the nanosponges were formulated with good stability.

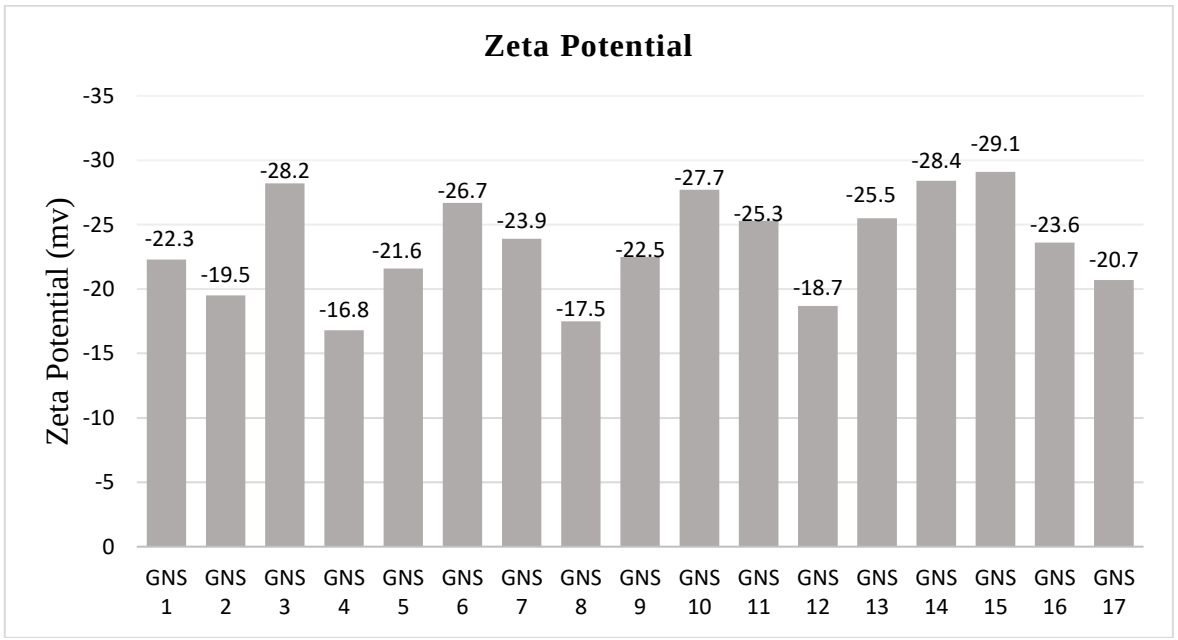

Figure8: Zeta potential of Prepared Glimepiride Nanosponges

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1S (2024)
http://www.veterinaria.org
Article Received: Revised: Accepted:

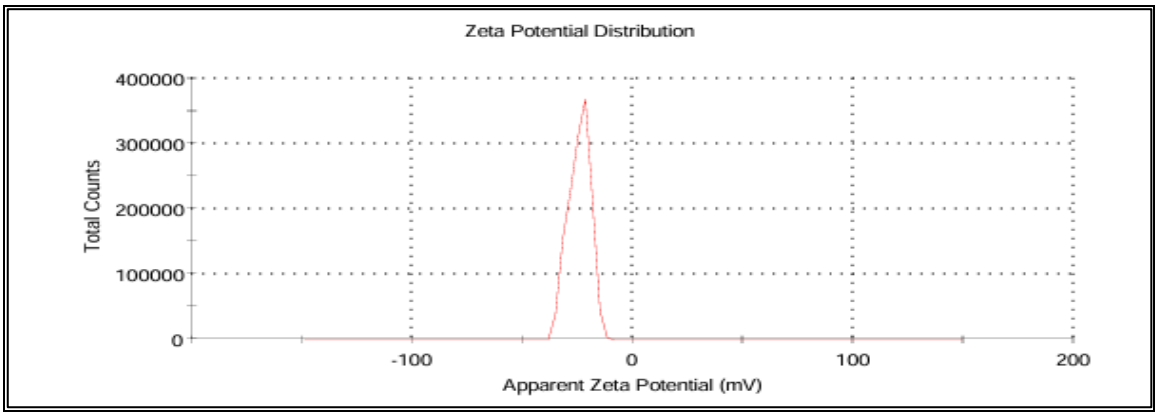

Figure 9: Zeta Potential of GNS 7

3.4 Entrapment efficiency

Percentage entrapment efficiency has been determined to verify that an efficient amount of Glimepiride was entrapped in the nanosponges. Nanosponges with % Entrapment Efficiency ranging from 86.4±1.7 to 97.4±1.1% were produced. The % Entrapment Efficiency data of prepared nanosponges is displayed in Table 4 & Figure 10.

Table 4: The % Entrapment Efficiency of prepared Glimepiride Nanosponges

S.No.	Formulation code	Entrapment Efficiency (%)
1	GNS 1	92.3±2.1
2	GNS 2	95.3±1.8
3	GNS 3	88.7±2.5
4	GNS 4	94.4±2.6
5	GNS 5	96.6±1.5
6	GNS 6	93.9±1.2
7	GNS 7	97.4±1.1
8	GNS 8	94.2±2.1
9	GNS 9	89.4±2.2
10	GNS 10	96.3±1.6
11	GNS 11	93.8±1.7
12	GNS 12	91.1±1.4
13	GNS 13	90.9±1.6
14	GNS 14	92.2±2.2
15	GNS 15	86.4±1.7
16	GNS 16	96.2±0.9
17	GNS 17	93.3±1.5

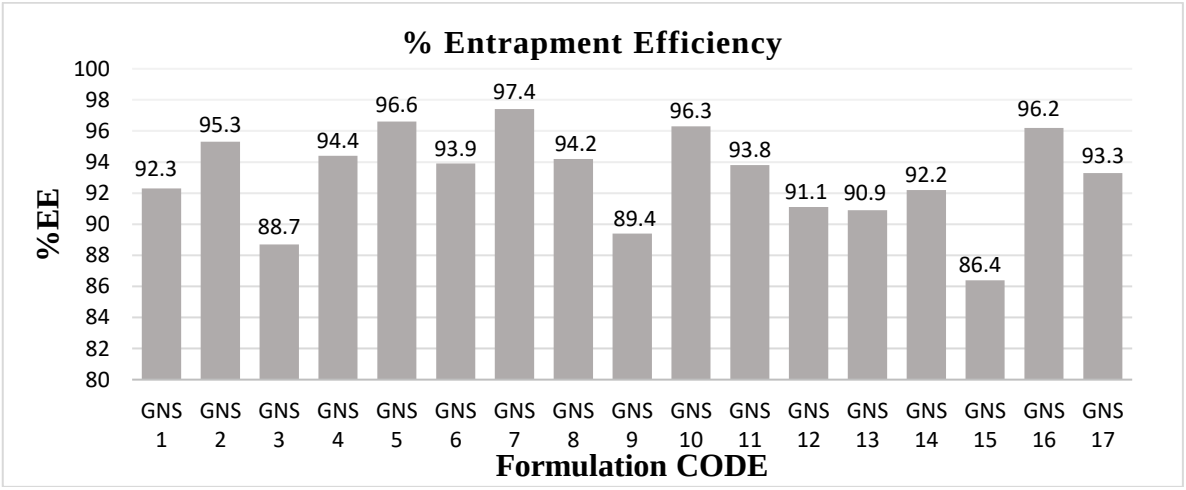

Figure 10: %EE of Prepared glimepiride Nanosponges

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1S (2024)
http://www.veterinaria.org
Article Received: Revised: Accepted:

3.5 SEM Analysis

Scanning Electron Microscopy was used to examine the morphology of the chosen optimum formulation of Glimepiride nanosponges. Figure 11 displays SEM image of the GNS 7 nanosponges. It was found that the nanosponges were uniformly spherical, nanoscale particles having a porous and spongy texture. The inward tunneling of the pores might be attributed to the diffusion of Dichloromethane during the manufacturing process from the nanosponges' surface.

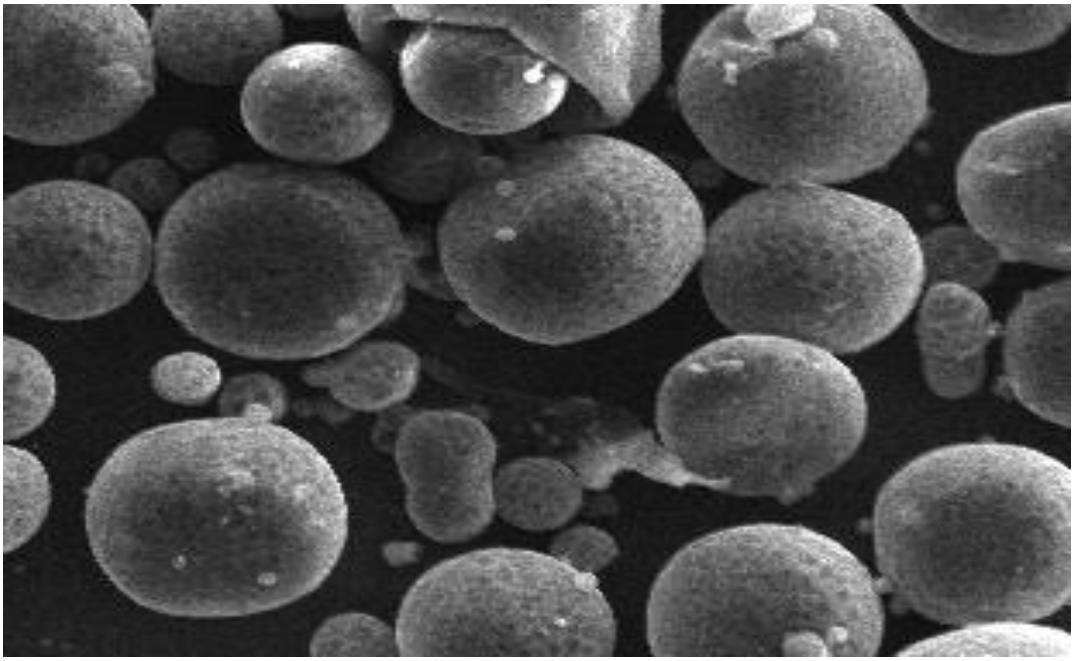

Figure 11: SEM Analysis of Glimepiride Nanosponges

3.6 FTIR Interaction Study

To verify the compatibility of the medicine Glimepiride and polymer ethyl cellulose employed in the formulation of nanosponges, Fourier transform infrared spectroscopy (FT-IR) investigation was conducted for independent drug and polymer, and for drug and polymer physical mixtures. Spectra obtained using FT-IR at wave numbers between 4000 and 400 cm-^{1}are reported in Table 7.

Table 7: FT-IR Interpretation of Glimepiride functional group

Functional group	Theoretical wave number	Reported wave number
C=O stretch of amide	1650-1760 cm^{-1}	1711.10 cm^{-1}
N-H Stretching:	3300-3500 cm^{-1}	3472.21 cm^{-1}
N-H Bending:	1500-1650 cm^{-1}	1539.32 cm^{-1}
Sulfonyl group (SO_2)	1350-1390 cm^{-1}	1374.53 cm^{-1}
C=C stretching in Benzene ring	1400-1600 cm^{-1}	1445.98 cm^{-1}

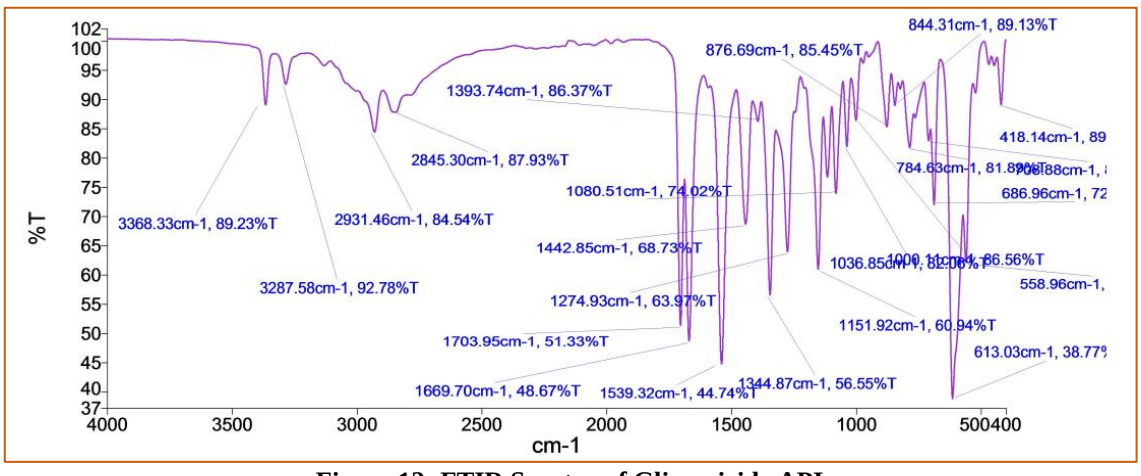

Figure 12: FTIR Spectra of Glimepiride API

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1S (2024)
http://www.veterinaria.org
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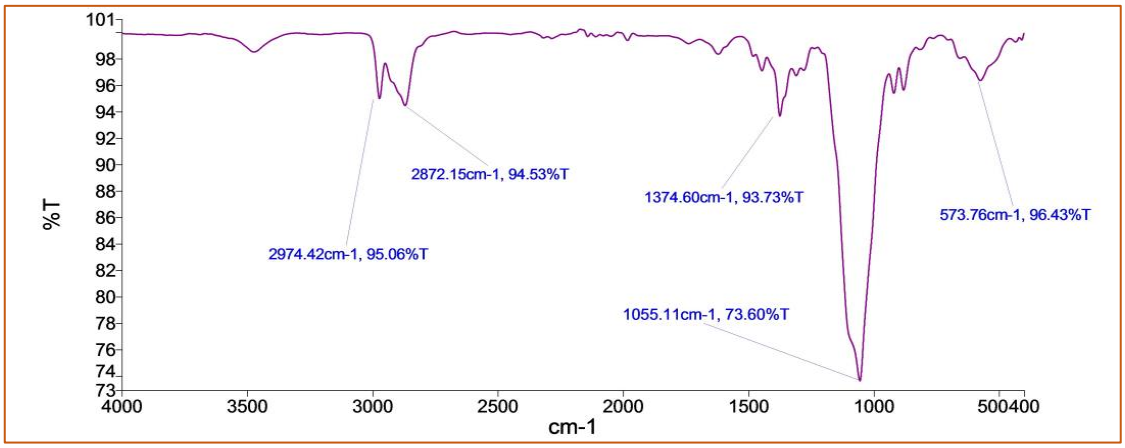

Figure 13: FTIR Spectra of Ethyl Cellulose

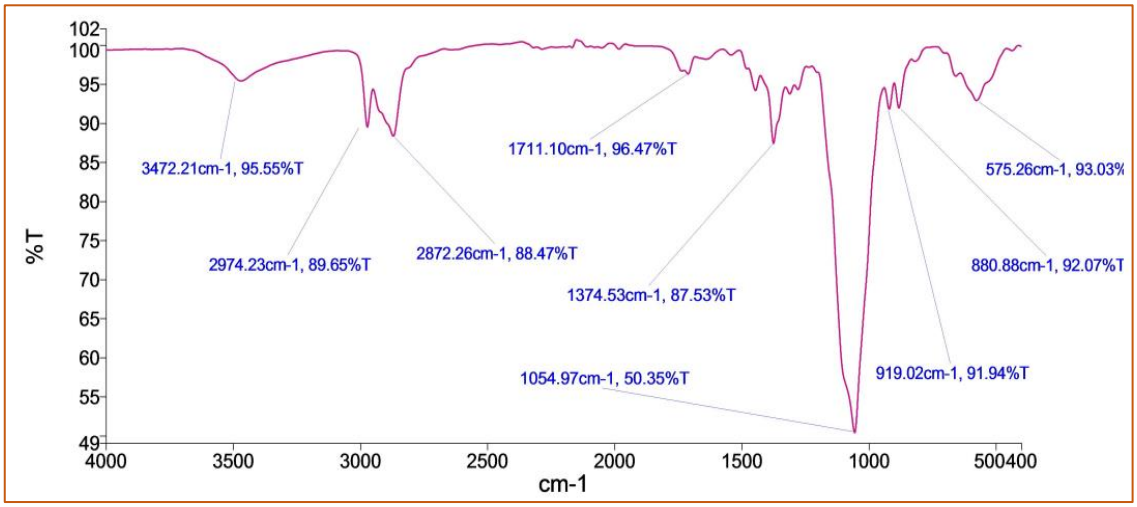

Figure 14: FTIR Spectra of Glimepiride Nanosponges (GNS 7)

3.7 *In-Vitro* Drug Release Study

The *in-vitro* drug release of several Glm nanosponges formulations over a dialysis membrane was studied, and graphs were subsequently created. Results showing the cumulative drug release percentage for GNS 5, GNS 7, GNS 10, and GNS 16 formulations with Glm encapsulated nanosponges are shown in Figure 15. The drug release investigation, which lasted up to 12 hours, discovered that the cumulative percentage of drug release (CPDR) for several formulations varied between 90.18 and 97.37%. Zero-order release was observed in all of the formulations. Because it demonstrated a substantially different performance from the pure drug suspension in Phosphate buffer ($p < 0.05$, t-test) and had the highest drug release percentage (97.37 ± 1.32%) after 12 hours, GNS 7 was chosen as the best formulation.

3.8 Storage stability evaluation of Glm Nanosponges:

In a stability chamber, the physical storage stability test was conducted for three months at 4±1 °C, 25±1 °C, and 45±1 °C with 75% relative humidity following ICH guidelines. Results indicate that while stored at 4°C and 25°C for three months, the physical properties of Glm Nanosponges formulation remained intact. In all circumstances, the particle size of all formulations grew over time (Figure 16). At 45±1 °C, the particle size expanded more than it did at 25±1 °C or 4±1 °C. All formulations, however, displayed a limited size distribution (PDI < 0.5). The fusion and aggregation of nanosponges during storage could cause the size to increase. When held at 4±1°C, 25±1 °C, and 45 ± 1 °C temperatures, respectively, the Glm content in nanosponges (Figure 17) and % EE (Figure 18) after three months were determined. Higher temperatures affected drug content more. It was also determined that the shelf-life of Glm nanosponges was 965 days at 4±1 °C, 554 days at 25±1 °C, and 213 days at 45±1°C.

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1S (2024)
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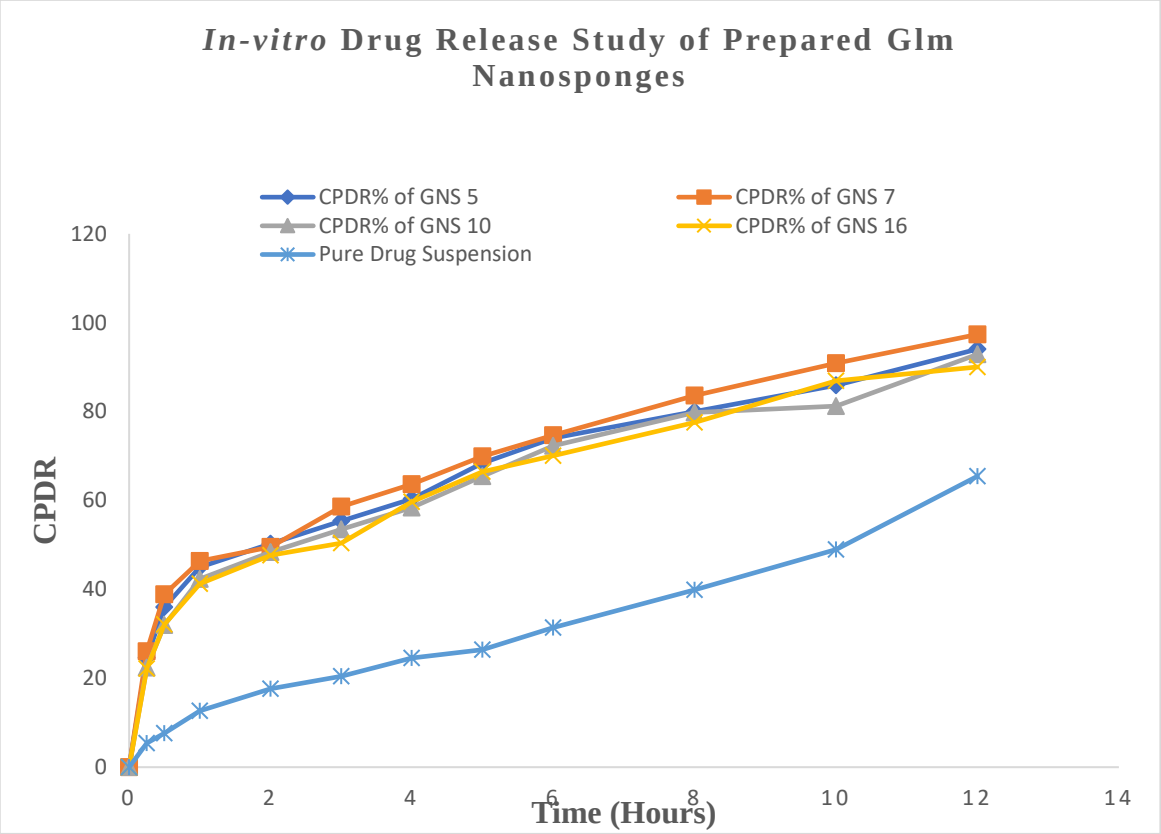

Figure 15: *In-Vitro* Drug Release Study of Prepared Glm Nanosponges

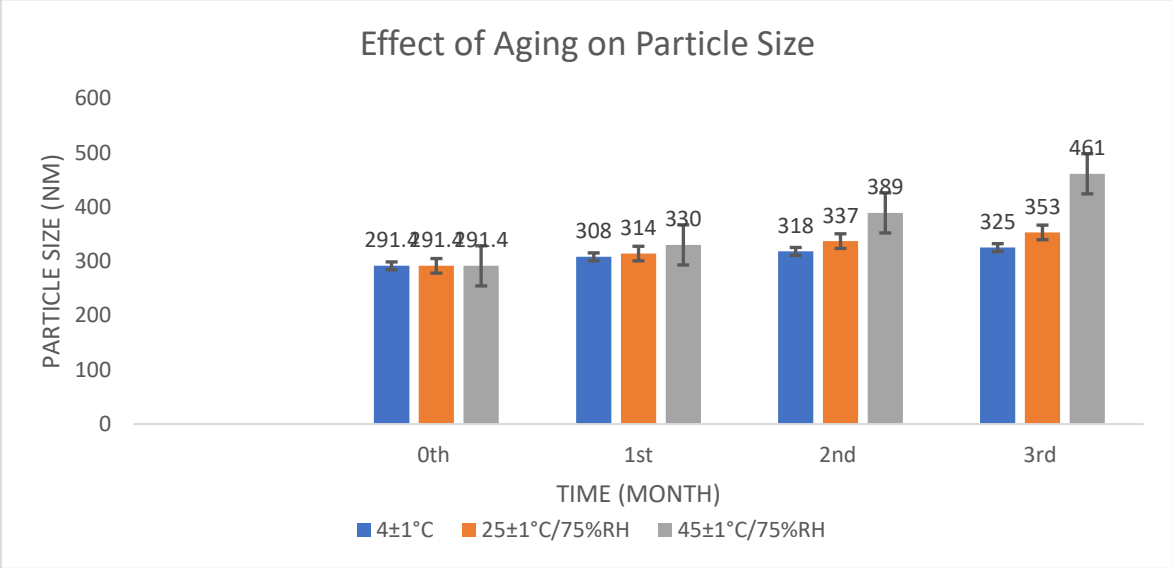

Figure 16: Effect of Aging on Particle Size of Nanosponges

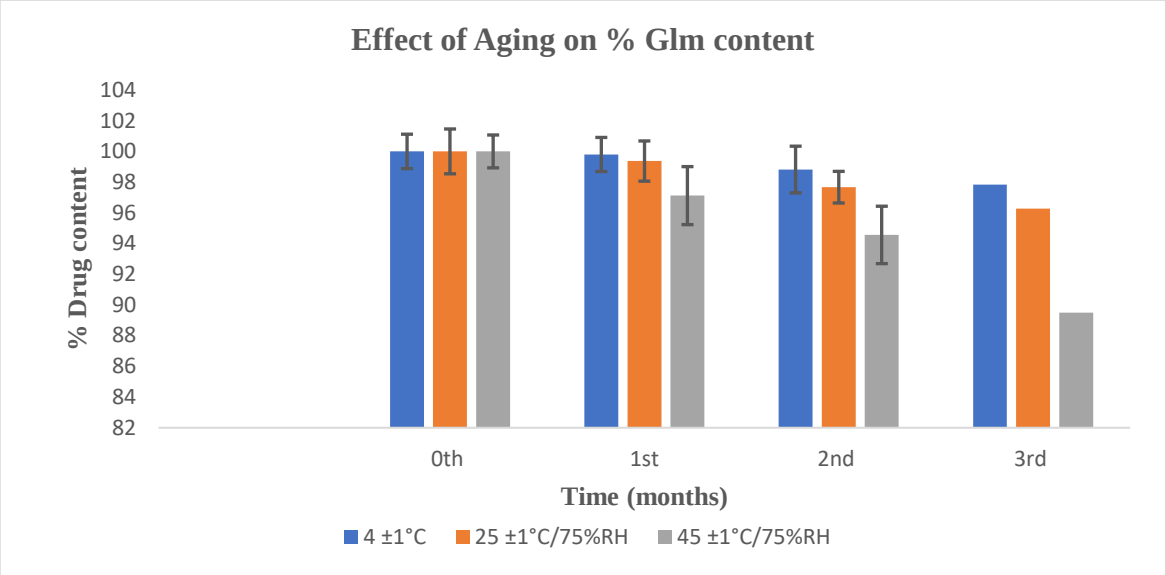

Figure 17: Effect of Aging on % Glm content of Nanosponges

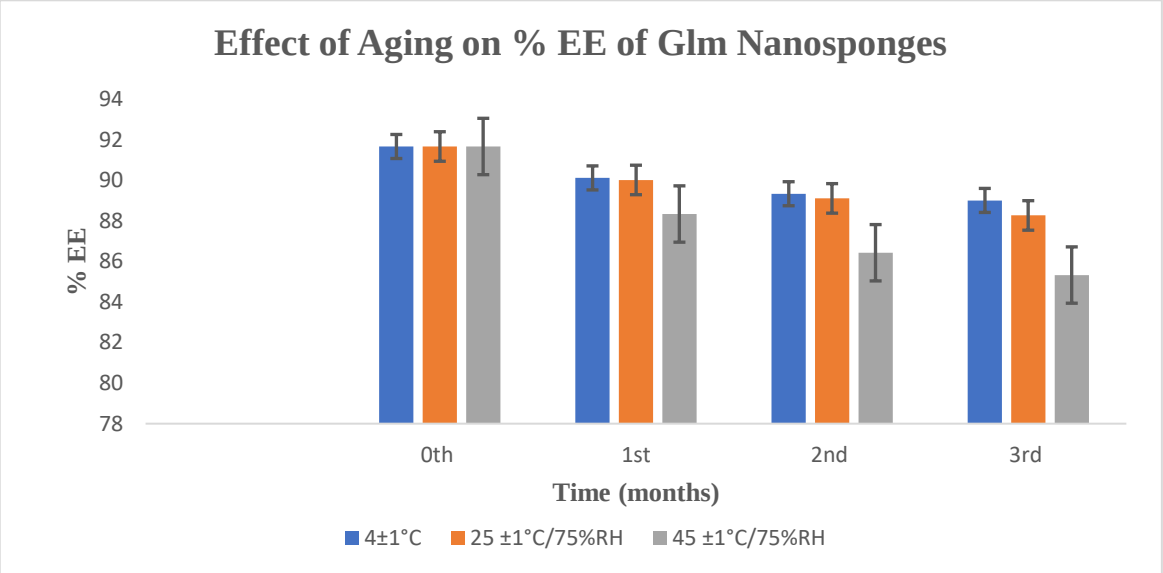

Figure 18: Effect of Aging on % EE of Glm Nanosponges

CONCLUSION

A chronic metabolic disease marked by elevated blood sugar levels is called diabetes mellitus. Type 2 diabetes is brought on by an improper insulin response, whereas Type 1 diabetes is brought on by inadequate insulin synthesis. Neural damage, heart disease, kidney failure, and visual issues might result from the syndrome. Medication, exercise, and dietary changes are utilized to treat diabetes. Glimepiride-based nanosponges have demonstrated encouraging outcomes in terms of increasing bioavailability, wettability, solubility, and dissolving rate. The drug was entrapped in nanosponges, and many characteristics were assessed, including production yield, zeta potential, FTIR, SEM, and particle size as well as entrapment efficiency. The nanosponges' polydispersity index ranged from 0.282 to 0.527, and their particle diameters ranged from 291 to 412 nm. The investigation using FT-IR spectroscopy revealed that the drug was entrapped in nanosponges. Thus, in the present study, Glimepiride nanosponges were successfully developed and evaluated for improved delivery of Glm with increased stability, low toxicity, and controlled drug release for better patient compliance.

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