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DEVELOPMENT AND CHARACTERIZATION OF NANOSPONGES CONTAINING GLICLAZIDE

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ABSTRACT

Abstract

The present study aims to develop and characterize Gliclazide-loaded nanosponges to overcome the drug's poor aqueous solubility and achieve sustained release for improved oral delivery. Gliclazide, a second-generation sulfonylurea used in the treatment of Type 2 Diabetes Mellitus, is limited by its low solubility and variable gastrointestinal absorption. Nanosponges, known for their porous, nanoscale structure, offer a promising platform for enhancing drug loading, stability, and controlled release. In this study, nanosponges were formulated using Eudragit S-100 as a polymer and polyvinyl alcohol (PVA) as a stabilizer by the emulsion solvent diffusion method. Six formulations (F1–F6) were prepared by varying polymer and stabilizer concentrations. The optimized formulation (F3) demonstrated the highest percentage yield (81.12%) and entrapment efficiency (79.85%), with favorable particle size and zeta potential, confirming its nanoscale nature and stability. Scanning Electron Microscopy (SEM) revealed spherical, porous nanosponges with uniform morphology. In-vitro drug release studies showed that Gliclazide nanosponges provided sustained release up to 12 hours, compared to rapid release from the pure drug. Drug release kinetics indicated that the optimized formulation followed First Order and Higuchi models with non-Fickian diffusion behavior. These results suggest that nanosponge-based formulations can be a promising alternative for enhancing the therapeutic performance of poorly soluble antidiabetic agents like Gliclazide.

Keywords: Gliclazide, Nanosponges, Sustained Release, Eudragit S-100, Emulsion Solvent Diffusion, Entrapment Efficiency, In-vitro Drug Release, Type 2 Diabetes Mellitus**.**

INTRODUCTION

Oral drug delivery remains the most preferred and convenient route of administration for therapeutic agents due to its non-invasiveness, patient compliance, and cost-effectiveness. However, a major challenge in oral drug delivery lies in the formulation of drugs that exhibit low aqueous solubility, poor bioavailability, and variable gastrointestinal (GI) absorption (Bansal *et al.*, 2011). According to the Biopharmaceutics Classification System (BCS), more than 40% of new chemical entities are classified as Class II drugs, characterized by low solubility and high permeability (Amidon *et al.*, 1995). One such drug is Gliclazide, a second-generation sulfonylurea widely used in the

treatment of Type 2 Diabetes Mellitus (T2DM).

Gliclazide works primarily by stimulating insulin secretion from pancreatic β-cells and has additional benefits including antioxidant, anti-inflammatory, and anti-platelet aggregation properties, which make it suitable for diabetic patients at risk of cardiovascular complications (Rosenstock *et al.,* 2004). However, despite its therapeutic effectiveness, the clinical utility of Gliclazide is limited due to its low water solubility (0.019 mg/mL), poor dissolution profile, and short biological half-life (~10–12 hours), which necessitates frequent dosing and leads to fluctuations in plasma drug concentration (Tiwari & Tiwari, 2010). These limitations can result in reduced patient adherence, suboptimal glycemic control, and increased risk of side effects such as hypoglycemia.

To overcome these challenges, novel drug delivery systems are increasingly being explored. One such emerging technology is the use of nanosponges—a class of nanosized, porous, and hyper-crosslinked polymeric carriers that can encapsulate both hydrophilic and lipophilic drugs, enhance drug solubility, and provide controlled or sustained release profiles (Trotta *et al.,* 2009). Nanosponges possess a unique 3D structure with internal nanocavities that can trap active molecules and release them in a controlled manner, improving drug stability, permeability, and targeting while minimizing systemic toxicity (Chaudhari *et al.,* 2014).

Typically, nanosponges are synthesized using biodegradable polymers such as β-cyclodextrin, ethyl cellulose, polylactic acid (PLA), and polyvinyl alcohol (PVA), which are crosslinked with agents like carbonyldiimidazole, diphenyl carbonate, or diisocyanates. These carriers are known for their high surface area, tunable particle size, excellent encapsulation efficiency, and biocompatibility, making them ideal for oral and transdermal delivery (Swaminathan *et al.,* 2010; Ansari *et al.,* 2020). In recent years, nanosponges have shown promising results in the delivery of various poorly soluble drugs such as paclitaxel, curcumin, and itraconazole, demonstrating enhanced solubility, absorption, and therapeutic index (Shah *et al.,* 2012).

Applying this innovative platform to Gliclazide offers several potential advantages. By encapsulating Gliclazide in nanosponges, it is possible to enhance its solubility, protect it from degradation, and prolong its release, thereby achieving a more consistent plasma concentration, reduced dosing frequency, and improved patient compliance. Moreover, nanosponges can be designed to release the drug preferentially in the intestinal environment, where Gliclazide absorption is optimal (Jain *et al.,* 2018).

The present study focuses on the development and characterization of Gliclazide-loaded nanosponges with the objective of overcoming its physicochemical limitations and optimizing its delivery for improved glycemic control. The nanosponges will be prepared using a suitable polymer and crosslinking agent via the emulsion-solvent diffusion or quasi-emulsion method. The formulations will be evaluated for particle size, drug loading, entrapment efficiency, surface morphology (via SEM), in-vitro drug release, and drug release kinetics, to determine the suitability of nanosponges as a

sustained-release oral delivery system for Gliclazide.

MATERIAL AND METHODS

Materials

The materials employed in the formulation of Gliclazide-loaded nanosponges were of analytical grade and selected based on their compatibility and functional roles in nanosponge development. Gliclazide, the active pharmaceutical ingredient, was obtained as a gift sample from Bioplus Life Sciences, Bangalore**.** Polymers such as Poly-methyl-methacrylate (PMMA) were procured from Research Lab Fine Chem Industries, Mumbai**,** and Eudragit S-100 from Evonik Industries, Mumbai**,** both serving as structural materials in nanosponge formation. Dibutyl phthalate, used as a plasticizer, was supplied by Loba Chemie Pvt. Ltd., Mumbai**.** Organic solvents including ethanol**,** dichloromethane**,** methanol, and chloroform were purchased from Qualigens Fine Chemicals, Mumbai**,** essential for the emulsification and solvent diffusion methods. Buffer components such as disodium hydrogen phosphate**,** dipotassium hydrogen orthophosphate**,** and sodium chloride were obtained from S. D. Fine Chem. Ltd., Mumbai**,** and used for preparing the phosphate buffer solution required in drug release studies.

Methods

Formulation Development of Nanosponges

Gliclazide nanosponges were prepared by different proportions of Eudragit S-100, polyvinyl alcohol by emulsion solvent diffusion technique (Shameem *et al.*, 2020). The disperse phase consisting of 10mg Gliclazide and specified quantity of Eudragit S-100 (Table 1) dissolved in 30 mL of dichloromethane was slowly added to a definite amount of PVA in 100 mL of aqueous continuous phase. The mixture was stirred at 1000 rpm on a magnetic stirrer for two hours. The formed Gliclazide nanosponges were collected by vacuum filtration and dried in an oven at 40°C for 24 hrs.

Table 1: Composition of Gliclazide nanosponges

Ingredients	F1	F2	F3	F4	F5	F6
Gliclazide (mg)	10	10	10	10	10	10
Polyvinyl alcohol (mg)	200	300	400	500	600	800
Eudragit S-100 (mg)	100	150	200	250	300	350
Dichloromethane	15	15	15	15	15	15
Distilled water (ml)	100	100	100	100	100	100

Characterization of Nanosponges

Percentage yield

The Gliclazide nanosponges obtained after drying was weighed. Percentage yield value was calculated as follows:

$$\% \text{ yield} = \text{Weight of nanosponges} \times 100 / \text{Total solids weight}$$

Entrapment efficiency

UV spectrophotometric method was used to estimate entrapment efficiency of Gliclazide nanosponges. A calibration curve was plotted for Gliclazide in pH 7.2 phosphate buffer in the range of 5-25 µg/mL (Beer's Lambert's range) at 230nm (Waghmare *et al.*, 2017).

A good linear relationship was observed between the concentration of Gliclazide and its absorbance (r^2=0.999, m=0.030, n=3). 10 mg of Gliclazide nanosponges of each batch were selected, powdered in a mortar and placed in 10 mL of pH 7.2 phosphate buffer. Gliclazide was extracted by centrifuging at 1000 rpm for 30 min, filtered and analyzed concentration from calibration curve data after necessary dilution. Percentage entrapment was calculated as follows:

% Entrapment efficiency= Actual drug

Particle size, polydispersity index

Average particles size, polydispersity index (PDI) of prepared nanosponges was determined using Zetasizer (DTS were 4.10, Horriba instrument, India). The nanosponges formulation was diluted with deionized water (1:9 v/v) and analysed for average size and PDI (Richhariya *et al.*, 2015).

Shape and surface morphology

The shape and surface morphology of the nanospongess were investigated using scanning electron microscopy (IISER, Bhopal). The nanospongess were fixed on supports with carbon-glue, and coated with gold using a gold sputter module in a high-vacuum evaporator. Samples were then observed with the Scanning Electron Microscope at 10 kV.

***In vitro* drug release from nanosponges**

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. The test determines the time required for formulation to release percentage of drug under specified conditions (Patil *et al.*, 2017).

Dissolution Parameters

Medium	900ml, pH 7.2 Phosphate Buffer
Apparatus	Paddle (USP-II)
RPM	55
Temperature	37°C±0.5
Time Points	0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs.

Procedure: For the oral dosage forms the *in vitro* dissolution study must be conducted in the dissolution medium which simulate the in-vivo conditions (actual physiological conditions). The *in vitro* drug release studies for the prepared formulation were conducted for a period of 12 hrs using an Labindia DS 8000 model dissolution tester USP Type-2 apparatus (rotating paddle) set at 100 rpm and a temperature of 37± 0.5°C formulation was placed in the 900ml of the medium. At specified intervals 5ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 230nm for the presence of model drug, using a UV-visible spectrophotometer.

Mathematical treatment of *in-vitro* release data: The quantitative analysis of the values

obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used.

Zero Order kinetics: The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_t = Q_o + K_o t$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most times, Q_o=0) and K_o is the zero order release constant.

First Order kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_1 is the zero order release constant.

In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

Higuchi Model: Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The simplified Higuchi model is expressed as:

$$Q = K_H \cdot t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms such as transdermal systems and matrix tablets with water-soluble drugs.

Korsmeyer Peppas Model: Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\, t^n$$

Where M_t/M_∞ is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of *n* =0.5 for fickian diffusion and higher values of *n*, between 0.5 and 1.0, or *n* =1.0, for mass transfer following a non-fickian model. In case of a cylinder *n* =0.45 instead of 0.5, and

0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent *n* the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (*l*) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{t-l}}{M_\infty} = a\,(t-l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

In the absence of lag time or burst effect, l and b value would be zero and only at^n is used. This mathematical model, also known as *Power Law*, has been used very frequently to describe release from several different pharmaceutical modified release dosage forms.

RESULTS AND DISCUSSION

The current study focused on the formulation and characterization of Gliclazide-loaded nanosponges using Eudragit S-100 and polyvinyl alcohol (PVA) via the emulsion solvent diffusion technique. The goal was to enhance the entrapment efficiency, solubility, and sustained drug release profile of Gliclazide, a BCS Class II drug.

Six nanosponge formulations (F1–F6) were developed by varying the ratios of Eudragit S-100 and PVA, as shown in Table 1. The percentage yield of nanosponges (Table 2) ranged from 70.25% (F6) to 81.12% (F3). The highest yield in F3 can be attributed to the optimal polymer-surfactant balance, promoting efficient emulsification and particle formation. Formulations with higher PVA (e.g., F6) may have resulted in excessive viscosity, leading to reduced yield due to difficulty in phase separation and filtration.

Entrapment efficiency (EE%) of Gliclazide nanosponges is shown in Table 3. Among all, F3 showed the highest EE (79.85% ± 0.14). This suggests that an optimal concentration of Eudragit S-100 (200 mg) allows the formation of a more stable matrix, which facilitates efficient encapsulation of the drug. A decrease in EE% in F6 and F1 may result from either insufficient matrix formation or drug diffusion into the external aqueous phase during preparation.

The mean particle size distribution of the optimized formulation (F3) is illustrated in Figure 4, confirming nanoscale size suitable for oral delivery. Zeta potential measurements (Figure 5) indicated good electrostatic stability of the nanosponges. A stable zeta potential ensures that the particles remain suspended and do not aggregate, which is essential for improved bioavailability and dispersion.

The surface morphology studied through Scanning Electron Microscopy (SEM) (Figure 6) confirmed the spherical, porous nature of the nanosponges. The uniform surface texture and absence of significant agglomeration demonstrate successful fabrication and suggest high surface area, which may contribute to improved drug loading and release characteristics.

The drug release profile of pure Gliclazide and the nanosponge formulation is presented in Table 4. While the pure drug exhibited rapid release (over 90% within 2 hours), the nanosponge formulation provided a sustained release up to 12 hours (98.85%), confirming its potential for controlled delivery. This controlled release behavior helps in maintaining therapeutic plasma levels of Gliclazide over a prolonged duration, potentially reducing the frequency of dosing and improving glycemic control in diabetic patients.

The release kinetics of optimized formulation F3 were analyzed using multiple kinetic models (Table 6). The drug release followed First Order kinetics (R^2 = 0.9560) and also fitted well to the Higuchi model (R^2 = 0.9551), indicating a diffusion-controlled release mechanism. Additionally, the Korsmeyer-Peppas model (R^2 = 0.9345) suggested a non-Fickian (anomalous) diffusion, meaning the drug release was governed by both diffusion and polymer matrix erosion. The processed data used to derive the release kinetics is tabulated in Table 5, including log-transformed values for various kinetic model fittings.

Table 2: Percentage yield for different formulation

Formulation	Percentage Yield*
F1	73.32±0.15
F2	76.65±0.74
F3	81.12±0.32
F4	72.23±0.15
F5	73.32±0.22
F6	70.25±0.41

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

Table 3: Entrapment Efficiency for Different Formulation

Formulation	% Entrapment Efficiency of prepared nanosponges
F1	68.23±0.25
F2	72.45±0.32
F3	79.85±0.14
F4	68.74±0.22
F5	69.63±0.52
F6	66.12±0.36

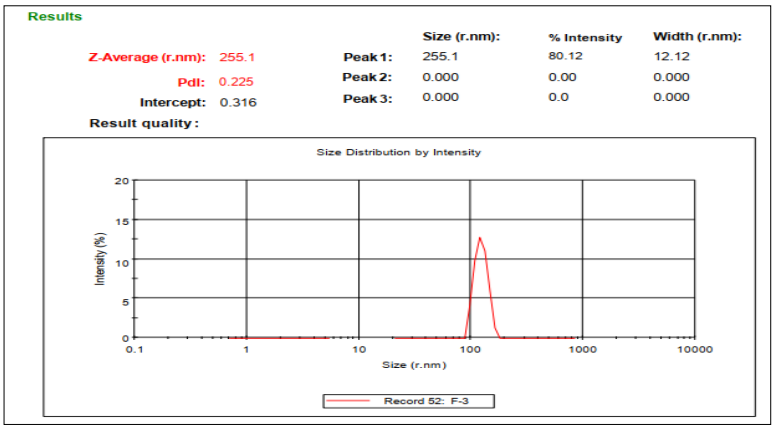

Figure 1: Measurement of mean particle size

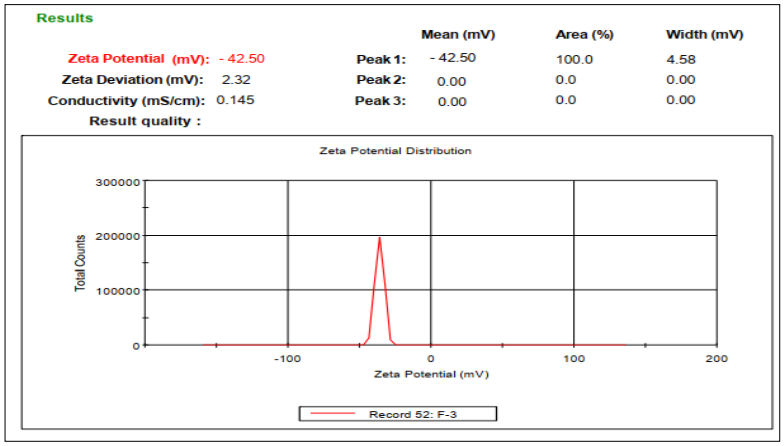

Figure 2: Graph of zeta potential

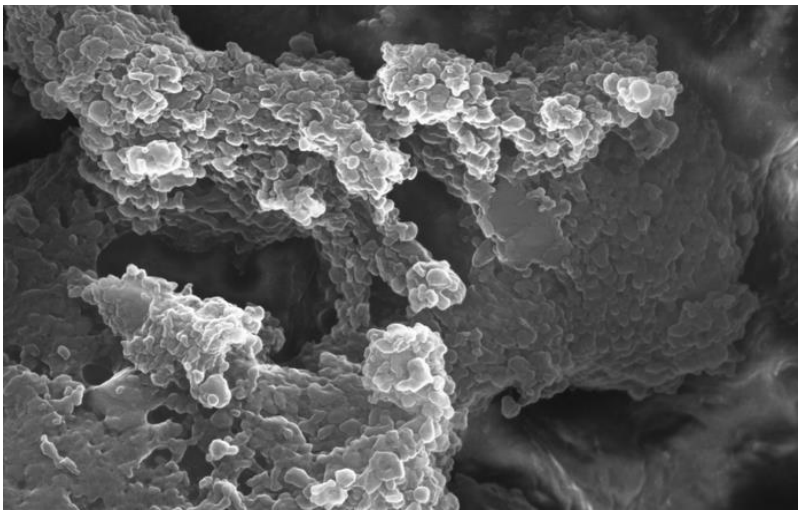

Figure 3: Scanning electronic microscopy of optimized formulation (F3)

Table 4: *In vitro* drug release study of Gliclazide loaded nanosponges

S. No.	Time (hrs.)	Plain Drug	Nanosponges
1.	0.5	26.65	11.25
2.	1	45.65	26.65
3.	1.5	67.98	32.22
4.	2	92.23	46.65
5.	3	-	58.85
6.	4	-	69.99
7.	6	-	76.65
8.	8	-	88.85
9.	12	-	98.85

Table 5: *In-vitro* drug release data for optimized formulation F3

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	11.25	1.051	88.75	1.948
1	1	0	26.65	1.426	73.35	1.865
1.5	1.225	0.176	32.22	1.508	67.78	1.831
2	1.414	0.301	46.65	1.669	53.35	1.727
3	1.732	0.477	58.85	1.770	41.15	1.614
4	2	0.602	69.99	1.845	30.01	1.477
6	2.449	0.778	76.65	1.885	23.35	1.368
8	2.828	0.903	88.85	1.949	11.15	1.047
12	3.464	1.079	98.85	1.995	1.15	0.061

Table 6: Regression analysis data of Gliclazide loaded nanosponges

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
F3	0.8494	0.9560	0.9551	0.9345

CONCLUSION

The present study successfully demonstrated the formulation and evaluation of Gliclazide-loaded nanosponges using the emulsion solvent diffusion method. Among the six formulations developed, F3 emerged as the optimized batch, showing maximum percentage yield (81.12%), high entrapment efficiency (79.85%), and a sustained drug release profile extending up to 12 hours. The nanosponge system exhibited favorable physicochemical properties including

desirable particle size, zeta potential, and morphology, as confirmed by SEM and particle analysis studies. The in-vitro release kinetics followed a First Order and Higuchi model, suggesting that the drug release was primarily governed by diffusion mechanisms. Furthermore, the Korsmeyer-Peppas model indicated a non-Fickian release pattern, implying that both drug diffusion and polymer erosion contributed to the release process.

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