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Design And Development Of Sustain Release Nanosponges Formulation Of Rosiglitazone

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Abstract
The present study focuses on the design and development of a sustained release nanosponge formulation of Rosiglitazone, an antidiabetic agent. Nanosponges were prepared using the emulsion solvent diffusion method, and various formulations (F1–F6) were evaluated for percentage yield, entrapment efficiency, particle size, zeta potential, and morphological characteristics. Among them, formulation F3 exhibited the highest entrapment efficiency (80.33 ± 0.15%) and optimum particle size (124.32 ± 0.45 nm). In vitro drug release studies indicated a sustained release pattern, with F3 achieving 98.85% cumulative release over 12 hours and following Higuchi kinetics (R^2 = 0.9543). Antidiabetic activity was evaluated by in vitro α-amylase inhibition assay, and F3 showed greater inhibition (IC_{50} = 13.96 µg/mL) compared to standard acarbose (IC_{50} = 17.57 µg/mL). Stability studies confirmed the physical and chemical stability of the optimized formulation under different storage conditions over three months. These findings suggest that nanosponge-based delivery of Rosiglitazone offers a promising approach for sustained antidiabetic therapy.
Keywords: *Rosiglitazone, Nanosponges, Sustained release, Entrapment efficiency, In vitro drug release, α-amylase inhibition, Higuchi kinetics, Antidiabetic activity, Stability studies.*

INTRODUCTION

Rosiglitazone, a member of the thiazolidinedione (TZD) class, is an oral antidiabetic agent that functions by activating peroxisome proliferator-activated receptor gamma (PPAR-γ), thereby enhancing insulin sensitivity in adipose tissue, skeletal muscle, and the liver. This mechanism makes it effective in managing type 2 diabetes mellitus by improving glycemic control in insulin-resistant individuals (Willson et al., 2000). Despite its proven therapeutic efficacy, Rosiglitazone suffers from poor aqueous solubility, limited bioavailability, and a relatively short biological half-life, necessitating frequent dosing to maintain effective plasma concentrations. These drawbacks can reduce patient adherence and lead to suboptimal therapeutic outcomes (Kim et al., 2004).

To overcome these challenges, novel drug delivery systems such as nanosponges are being investigated to provide sustained and controlled drug release. Nanosponges are porous, nanoscale carriers formed by cross-linked polymers typically based on cyclodextrins that can encapsulate both hydrophilic and lipophilic drugs. These systems offer several advantages including increased drug solubility, improved stability, controlled release profiles, and reduced dosing frequency (Trotta et al., 2012; Swaminathan et al., 2007) . Their high surface area and porous structure enable efficient drug loading and release modulation, making them ideal candidates for oral delivery of poorly water-soluble drugs like Rosiglitazone.

Trotta et al. have demonstrated that cyclodextrin-based nanosponges can act as effective carriers for sustained drug release, owing to their ability to form inclusion and non-inclusion complexes with a wide variety of active pharmaceutical ingredients. Similarly, Swaminathan et al. reported improved solubility and sustained release of itraconazole using nanosponge systems, highlighting their versatility across different drug classes (Trotta et al., 2012). These findings support the hypothesis that nanosponge technology can be extended to Rosiglitazone to enhance its biopharmaceutical profile.

Furthermore, Beg et al. emphasized the potential of nanosponges as promising platforms for targeted and sustained drug delivery. Their study outlined how nanosponges could improve therapeutic efficacy, reduce side effects, and enhance patient compliance in chronic therapies like diabetes (Beg et al., 2012). Given the chronic nature of type 2 diabetes and the need for stable glycemic control, a nanosponge-based formulation

of Rosiglitazone offers a strategic approach to prolong drug release, improve oral bioavailability, and minimize dosing frequency.

Hence, the present study is focused on the design, development, and evaluation of a sustained-release nanosponge formulation of Rosiglitazone, with the objective of overcoming its solubility and pharmacokinetic limitations. The formulation will be optimized and characterized for particle size, entrapment efficiency, in vitro release, and release kinetics to confirm its suitability for sustained oral drug delivery.

MATERIAL AND METHODS

Material

Rosiglitazone was received as a gift sample from a pharmaceutical company. Polymers such as poly-methyl-metha-acrylate and Eudragit S-100 were procured from Research Lab Fine Chem Industries and Evonik Industries, Mumbai, respectively. Dibutyl phthalate was obtained from Loba Chemie Pvt. Ltd., Mumbai. Solvents including ethanol, methanol, dichloromethane, and chloroform were supplied by Qualigens Fine Chemicals, Mumbai. Buffer components such as disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, and sodium chloride were purchased from S. D. Fine Chem. Ltd., Mumbai. All chemicals and reagents used were of analytical grade.

Methods

Formulation and Development of Nanosponges

Rosiglitazone nanosponges were prepared by different proportions of Eudragit S-100, polyvinyl alcohol and Pluronic F68 by emulsion solvent diffusion technique (Shameem *et al.,* 2020). The disperse phase consisting of 100 mg Rosiglitazone and specified quantity of Eudragit S-100 (Table 7.1) 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 Rosiglitazone nanosponges were collected by vacuum filtration and dried in an oven at 40^0C for 24 hrs.

Table 1: Composition of Rosiglitazone loaded nanosponges

Ingredients	F1	F2	F3	F4	F5	F6
Rosiglitazone (mg)	8	8	8	8	8	8
Polyvinyl alcohol (mg)	200	300	400	500	600	800
Eudragit S-100 (mg)	100	150	200	250	300	350
Pluronic F68 (mg)	100	100	100	100	100	100
Dichloromethane	15	15	15	15	15	15
Distilled water (ml)	100	100	100	100	100	100

Characterization of Nanosponges

Percentage yield

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

% yield = Weight of nanosponges×100/Total solids weight

Entrapment efficiency

UV spectrophotometric method was used to estimate entrapment efficiency of Rosiglitazone nanosponges (Waghmare *et al.,* 2017). A calibration curve was plotted for Rosiglitazone in pH 7.2 phosphate buffer in the range of 5-25 µg/mL (Beer's Lambert's range) at 228nm.

A good linear relationship was observed between the concentration of Rosiglitazone and its absorbance (r^2=0.999, m=0.030, n=3). 10 mg of Rosiglitazone nanosponges of each batch were selected, powdered in a mortar and placed in 10 mL of pH 7.2 phosphate buffer. Rosiglitazone 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 (Patil *et al.*, 2017).

***In vitro* drug release of 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 (Penjuri *et al.*, 2016).

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 228nm for the presence of model drug, using a UV-visible spectrophotometer.

***In-vitro* anti-diabetic activity**

Alpha amylase inhibition assay

Preparation of standard: 10mg acarbose was dissolved in 10 ml methanol, and various aliquots of 10-50µg/ml were prepared in methanol.

Preparation of sample: weight equivalent to 10mg of Rosiglitazone nanosponges add with 5ml methanol sonicate it for 10min, filter, and make up the volume up to 10ml. various aliquots of 10-50µg/ml were prepared in methanol for the estimation of enzyme inhibition.

Method: A total of 500 µl of test samples and standard drug (10-50µg/ml) were added to 500 µl of 0.20 mM phosphate buffer (pH 6.9) containing α-amylase (0.5mg/ml) solution and were incubated at 25°C for 10 min (Bernfeld, 1955). After these, 500 µl of a 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) was added to each tube. The reaction mixtures were then incubated at 25°C for 10 min. The reaction was stopped with 1.0 ml of 3, 5 dinitrosalicylic acid colour reagent. The test tubes were then incubated in a boiling water bath for 5 min, cooled to room temperature. The reaction mixture was then diluted after adding 10 ml distilled water and absorbance was measured at 540 nm. Control represent 100% enzyme activity and were conducted in similar way by replacing drug with vehicle.

Stability studies of optimized nanosponges formulation (F3)

The prepared nanosponges subjected to stability studies at 40±2°C/75±5% RH and 30±2°C/60±5% RH as per ICH guidelines for a period of 3 months. Samples were withdrawn at 1 month time intervals and evaluated for physical appearance and drug content.

RESULTS AND DISCUSSION

The nanosponges of rosiglitazone were successfully formulated using different polymer ratios, and the percentage yield and entrapment efficiency (EE) were evaluated. Among all formulations, F3 exhibited the highest percentage yield (82.23 ± 0.25%) and entrapment efficiency (80.33 ± 0.15%), indicating an optimal formulation process and polymer–drug interaction. This enhanced EE might be due to the appropriate polymer concentration and uniform encapsulation of the drug within the nanosponges.

Particle size analysis revealed a mean size in the nanometer range, with F3 showing an average of 124.32 nm, which is suitable for sustained release applications. The zeta potential of the formulation confirmed good physical stability due to the presence of surface charges, and SEM analysis showed a porous, spongy structure confirming successful nanosponge formation.

The in vitro drug release study indicated a sustained release profile for the nanosponges compared to plain rosiglitazone. The optimized formulation (F3) showed a cumulative drug release of 98.85% over 12 hours, whereas the plain drug demonstrated a rapid release (47.87% at 1 hour). The controlled release from nanosponges can be attributed to the porous matrix and polymer entrapment which hinder drug diffusion.

Kinetic modeling revealed that the release profile of F3 best followed the Higuchi model (R^2 = 0.9543), indicating diffusion-controlled drug release, and showed good fit with Korsmeyer–Peppas (R^2 = 0.939), suggesting a non-Fickian (anomalous) transport mechanism. This supports the sustained release behavior through both diffusion and erosion processes.

The in vitro antidiabetic study further highlighted the efficacy of the nanosponge formulation. F3 demonstrated a higher percentage inhibition of α-amylase enzyme activity compared to standard acarbose, with an IC_{50} of 13.96 µg/ml, significantly lower than that of acarbose (17.57 µg/ml). This enhanced inhibitory effect suggests better therapeutic potential of rosiglitazone when delivered via nanosponge formulation.

The stability study of F3 showed minimal changes in particle size and entrapment efficiency over a three-month period under refrigerated (4 ± 0.2°C) and room temperature (25–28 ± 2°C) conditions, with no observable change in physical appearance, indicating excellent physical and chemical stability.

Table 2: Percentage yield for different formulation

Formulation	Percentage Yield*	Entrapment Efficiency (%)
F1	70.23±0.35	68.85±0.32
F2	76.65±0.33	73.32±0.25
F3	82.23±0.25	80.33±0.15
F4	74.44±0.41	73.32±0.33
F5	79.98±0.28	75.52±0.18
F6	76.65±0.33	70.32±0.14

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

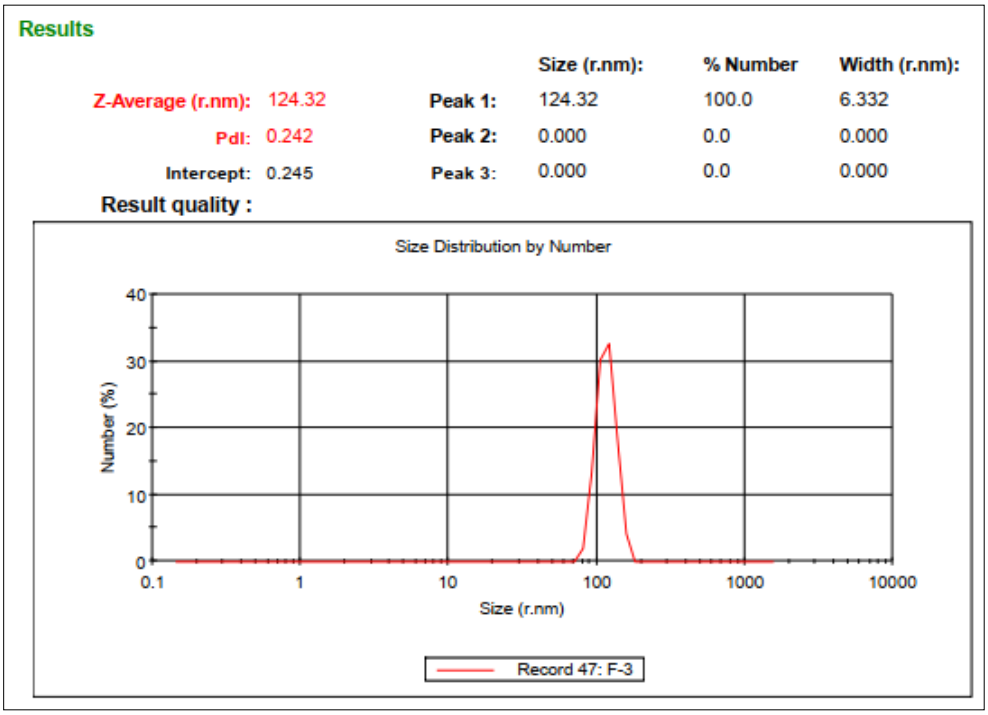

Figure 1: Measurement of mean particle size

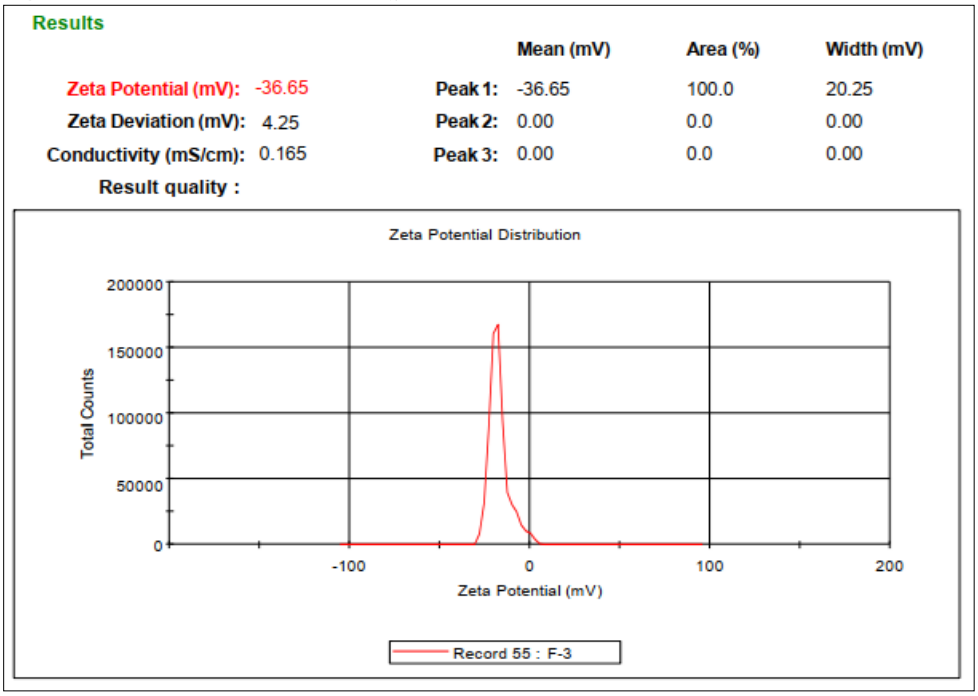

Figure 2: Graph of zeta potential

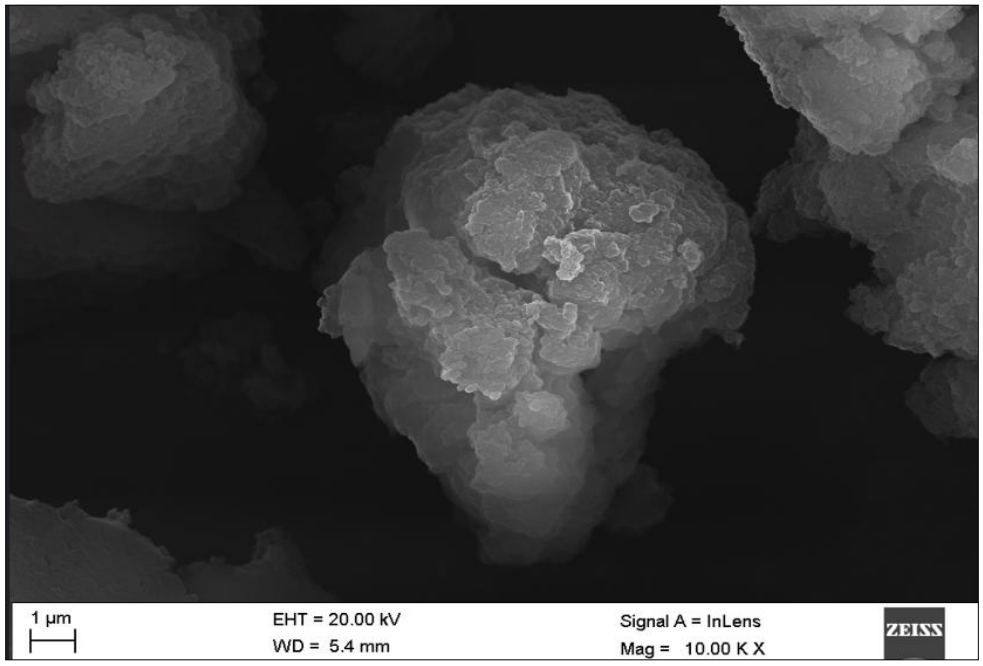

Figure 3: Scanning electronic microscopy of optimized formulation (F3)

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

		Cumulative % Drug Release	
S. No.	**Time (hrs.)**	**Plain Drug**	**Nanosponges**
1.	0.5	15.65	12.12
2.	1	47.87	23.32
3.	1.5	69.98	36.65
4.	2	79.98	47.78
5.	3	-	56.69
6.	4	-	69.95
7.	6	-	78.85
8.	8	-	85.55
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	12.12	1.084	87.88	1.944
1	1	0	23.32	1.368	76.68	1.885
1.5	1.225	0.176	36.65	1.564	63.35	1.802
2	1.414	0.301	47.78	1.679	52.22	1.718
3	1.732	0.477	56.69	1.754	43.31	1.637

4	2	0.602	69.95	1.845	30.05	1.478
6	2.449	0.778	78.85	1.897	21.15	1.325
8	2.828	0.903	85.55	1.932	14.45	1.160
12	3.464	1.079	98.85	1.995	1.15	0.061

Table 6: Regression analysis data of Rosiglitazone loaded nanosponges

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
F3	0.8472	0.9408	0.9543	0.939

Table 7: Results of % Inhibition of *in vitro* antidiabetic studies of standard Acarbose and Rosiglitazone-loaded nanosponges formulation F3

S. No.	Concentration (µg/ml)	% Inhibition	
		Acarbose	Rosiglitazone-loaded nanosponges formulation F3
1.	10	37.34	42.38
2.	20	53.57	55.94
3.	30	68.53	69.93
4.	40	83.92	85.31
5.	50	86.29	88.11
IC_{50} (µg/ml)		17.57	13.96

Table 8: Characterization of stability study of Optimized formulation (F3)

Characteristic	Time (Month)					
	1 Month		2 Month		3 Month	
Temperature	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C
Average particle size (nm)	124.32±0.45	125.65±0.25	125.95±0.36	126.55±0.15	128.85±0.22	130.32±0.15
% EE	80.33±0.15	75.65±0.85	79.98±0.92	74.45±0.88	78.85±0.65	72.25±0.74
Physical Appearance	Normal	Normal	Normal	Normal	Normal	Normal

CONCLUSION

The present study successfully developed and optimized rosiglitazone-loaded nanosponges with the aim of enhancing drug entrapment, sustaining drug release, and improving antidiabetic efficacy. Among the various formulations, F3 demonstrated superior performance with the highest percentage yield and entrapment efficiency, optimal particle size, and a sustained drug release profile extending up to 12 hours. The drug

release kinetics followed the Higuchi model, indicating a diffusion-controlled mechanism, further supported by the Korsmeyer–Peppas model suggesting anomalous transport.

In vitro antidiabetic activity of the optimized formulation (F3) revealed a significantly lower IC_{50} value compared to the standard drug acarbose, reflecting enhanced enzyme inhibition and therapeutic potential. The stability study further confirmed the formulation's robustness, with negligible variations in physical characteristics, particle size, and entrapment efficiency over three months under different storage conditions. Rosiglitazone-loaded nanosponges offer a promising nanocarrier system for sustained drug delivery and improved antidiabetic efficacy. This novel formulation could potentially overcome the limitations associated with conventional dosage forms of rosiglitazone and may serve as an effective approach in diabetes management upon further in vivo validation.

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