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Formulation and evaluation of Gliclazide loaded nanoparticles for management of diabetes

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Abstract
Diabetes mellitus (DM) is widely escalating chronic disease and most common in elder person. Gliclazide nanoparticles (GCZNPs) were prepared using solvent evaporation technique. Prepared nanoparticles were characterized for particle size, drug entrapment, *in vitro* drug release. The compatibility between drug and excipients was examined by Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC). The particle size of prepared GCZNPs was found to be in ranged from 295.5 to 720.04 nm. The drug entrapment efficiency of GCZNPs was in range 50.67 to 79.16 %. The percentage of drug loading was found 14.1 to 36.78. The optimized formulation, PLA 50 and PVA 0.45, 36.885 % of drug loading, resulted in 78.630 % of entrapment efficiency, particle size of 277.04 nm and released 75.43 % in 10 hrs. Conclusively, solid lipid nanoparticles of GCZ were successfully formulated with higher drug entrapment and could serve as promising delivery for poorly soluble drug.
Keywords: Diabetes Mellitus, Nanoparticles, Nanocarriers, Glucose.

1. Introduction

Diabetes is a complex set of metabolic disorder which has taken a radical increase affecting people of all age groups in the recent times. Type 2 diabetes is the commonest form and it developed when the body suffers from impaired ability to use insulin [1]. The conventional medications are mostly administered through the per oral route and come up with extrapyramidal side effects like hypoglycemia, weight gain, gastric intolerance, safety and efficacy issue. Thus, novel drug delivery systems are being developed and studied by researchers around the globe.

Gliclazide (GCZ) is a second generation antihyperglycemic agent used for treatment of non insulin dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues and acts by increasing basal insulin secretion as well as peripheral glucose utilization. GCZ also increase the sensitivity of insulin receptors and decrease hepatic gluconeogenesis [2]. The major drawback in the therapeutic application and efficacy of GCZ as an oral dosage form is its very low aqueous solubility with log P of 2.69, which leads to variable dissolution and absorption of the drug in the gastro-intestinal tract and ultimately causes variations in the bioavailability of the drug [3]. In market, GCZ is mostly available as oral formulations. GCZ is rapidly and well absorbed but is reported to have wide inter- and intra-individual variation in bioavailability [4]. Thus, there is a need to develop a formulation of GCZ that will reduce the inter- and intra-individual variability in absorption, thereby increasing its bioavailability by oral route.

One of the most popular approaches to improve the oral bioavailability of hydrophobic drug molecules is the utilization of lipid based drug delivery systems. The extensive research revealed the potential of lipid based formulations in enhancing drug bioavailability and therapeutic efficacy of the drug by various mechanisms viz; increasing luminal solublization of the drug, surpassing the first pass metabolism of drug by its transportation via lymphatic system, inhibition of Cytochrome P450-4A enzyme responsible for intestinal drug metabolism and inhibition of P-glycoprotein, an efflux transporter [5].

2. Material and Methods

2.1.Preformulation Studies and characterization of Gliclazide

2.1.1. Organoleptic Properties

"The look, colour, and smell of the medicinal material are among its organoleptic qualities. The identification and patient acceptance of gliclazide, a drug used to treat diabetes, depend on certain organoleptic features.

2.1.2. Solubility of Gliclazide

The solubility of gliclazide is checked in different solvent.

2.1.3. Melting point

The melting point of Gliclazide was measured using melting-temp apparatus equipped with a digital thermometer [6].

2.1.4. UV Spectrum

Determination of λ_{max}

For characterization of drug by UV spectroscopy, it was important to know wavelength of maximum absorption (λ_{max}). The wavelength of maximum absorption (λmax) in different solvent such as water, ethanol, phosphate buffer and methanol were observed.

2.1.5. HPLC Assay of Gliclazide

The drug was assayed using HPLC method reported by Rouini *et al.,* with slight modifications [7]. Mobile phase composed of acetonitrile: 0.4 µm distilled water (45%: 55%) of pH 3 adjusted by ortho-phosphoric acid. An aliquot of 20 µL sample was injected into HPLC column at a flow rate of 0.9 mL/min. The drug peak was detected at λ max = 230 nm at room temperature.

2.1.6. Fourier Transformation Infrared Analysis

FTIR of the Gliclazide was carried out for identification of drug by using KBr pellet method; a small quantity of drug was mixed with adequate quantity of IR grade KBr in mortar. The mix was then made into KBr pellets by hydraulic press. The samples were then analyzed in a double beam IR spectrometer with the scanning range of 4000 cm^{-1} - 400 cm^{-1}.

2.2.Preparation and optimization of Gliclazide nanoparticles (GCZNPs)

2.2.1. Preparation of Gliclazide nanoparticles

Nanoparticles containing Gliclazide were prepared by O/W solvent evaporation method. Accurately weighed quantity of drug was dissolved in dichloromethane (DCM) & acetone (5 ml each) and polymers in DCM (10 ml) separately and added into the aqueous phase (100 ml distilled water) containing surfactant polyvinyl alcohol (PVA) using magnetic stirrer, by adding organic phase into aqueous phase. Then the above emulsion was sonicated for 7 min. The emulsion was kept on magnetic stirrer for 3 - 4 hrs at room temperature for the evaporation of organic solvent, after that the nanoparticles were collected by centrifugation at 10000 rpm for 30 min. PVA is a water soluble surfactant, during centrifugation it was removed along with

decant. Trace amount of PVA present in nanoparticles were removed by washing with distilled water. After washing nanoparticles were lyophilized [8].

2.2.2. Optimization and experimental design

A number of preliminary experiments were conducted to determine the formulation parameters and conditions. To optimize the formulation a 3^2 full factorial design was applied for the preparation of inclusion complex using Design -Expert® Software (Version - 8.0.7.1), which allows evaluation by thirteen experiments, in order to limit the number of experiments [9]. The amount of polymers used as release retarding polymer (X1, mg) and PVA as a surfactant (X2, % w/v) with respect to drug were selected as independent variables. Such statistical models were used to evaluate the effect of independent variables on the dependent variables like particle size (Y1, nm), entrapment efficiency (Y2, %), drug loading (Y3, %). The actual and coded values of independent variables are shown in **Table 1, 2** along with their low coded (-1), medium (0) and high coded (+1).

Table 1: Variables in a 3^2 Full Factorial Design

Independent Variables	Level Used (Actual, Coded)					
	Low Actual	Medium Actual	High Actual	Low Coded	Medium coded	High Coded
X_1	50	100	150	-1.00	0.0p	1.00
X_2	0.15	0.3	0.45	-1.00	0.00	1.00

X1= Polymer concentration (mg)
X2= Surfactant concentration (%, w/v)

Dependent Variables

Particle size (nm)
Entrapment efficiency (%)
Drug loading (%)

Table 2: Batch Specifications of PLA Loaded Nanoparticles

Standard	Run	Factor - 1 Amount of Polymer PLA(mg) X1	Factor - 2 Amount of Surfactant PVA (%w/v) X_2
2	1	100	0.15
3	2	150	0.15
10	3	100	0.3
6	4	150	0.3
11	5	100	0.3
9	6	150	0.45
12	7	100	0.3
13	8	100	0.3
1	9	50	0.15

7	10	50	0.45
4	11	50	0.3
5	12	100	0.3
8	13	100	0.45

2.3. Characterization of Gliclazide Loaded PLA Nanoparticles

(a) Particle Size

Particle size analysis was conducted by photon correlation spectroscopy technique using Malvern Zetasizer. Gliclazide Loaded PLA Nanoparticles dispersions were appropriately diluted using Millipore filtered water (0.4µm) and measurements were conducted at a scattering angle of 173º [10].

(b) Percentage Entrapment Efficiency and Percentage Drug Loading

Entrapment efficiency and drug loading of various nanoparticles were calculated. Drug loading (%) and drug entrapment (%) were calculated by using formula:

$$\text{Entrapment Efficiency} = \frac{\text{Total amount of drug added} - \text{Amount of free drug}}{\text{Total amount of drug added}} \times 100$$

$$\text{Drug loading} = \frac{\text{Total amount of drug in formulation} - \text{Amount of free drug}}{\text{Weight of nanoparticles recovered}} \times 100$$

2.4.Characterization of Optimized Batch

a) Differential Scanning Calorimetry (DSC)

Thermal behaviour of nanoparticles was studied using DSC (Perkin Elmer Instruments). The samples were hermetically sealed in an aluminum pan. DSC traces were recorded between 30 and 250ºC with heating rate of 10°C/minute. Inert atmosphere was maintained by purging nitrogen at a flow rate of 10 mL/min. Control empty pan was placed at same atmospheric condition [11].

b) Fourier Transformation Infrared Analysis

FT-IR spectroscopy was performed for lyophilized nanoparticles. Samples were finely ground in a mortar and mixed with potassium bromide then pressed for 5 min at high pressure to form a disc. IR spectrum was then scanned over the range of 400 to 4000 cm^{-1}.

(c) *In-vitro* Drug Release Studies

The nanoparticles were evaluated *in- vitro* by using Dissolution Test Apparatus, Type- II at 37±0.5 ° C and at a paddle speed of 100 rpm. The Dissolution test was carried out in a 900 ml dissolution medium of phosphate buffer pH 6.8 up to 10 hrs. 5 ml samples were taken from the dissolution medium at different time intervals and drug release was determined with double beam ultraviolet spectrophotometer at 276 nm. The withdrawn samples were replenished with of fresh media [12].

c) Drug Release Kinetics

Data obtained from the *in-vitro* drug release studies were fit into various kinetics models such as zero order, first order and Higuchi model [13].

Zero-Order Model

Drug dissolution and release the drug can be represented by the equation:

$$Q_0 - Q_t = K_0 t \qquad (1)$$

Rearrangement of equation (1) yields:

$$Q_t - Q_0 + K_0 t \qquad (2)$$

Where Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$), Qt is the amount of drug dissolved in time t and K_0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted in graph as cumulative amount of drug released versus time.

First Order Model

This model has also been used to describe elimination and/or absorption of some drugs. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\log C = \log C_0 - K_t / 2.303 \quad (3)$$

In the above equation C_0 means the initial concentration of drug, the first order rate constant is k, and t is the time. The results are plotted as log cumulative percentage of drug present vs. time which forms a straight line with a slope of - K/2.303.

Higuchi Model

The model is depends on the hypotheses that (i) the concentration of drug present initially in the matrix is much higher than drug solubility; (ii) diffusion of drug takes place only in one dimension (edge effect must be negligible); (iii) drug particles size are much smaller than system thickness; (iv) dissolution and matrix swelling are negligible; (v) diffusivity is constant; and (vi) ideal sink conditions are always attained in the release environment. Accordingly, model expression is shown by the following equation:

$$f_t = Q = A\,[D(2C - C_s)\,C_s\,t]^{1/2} \quad (4)$$

Where Q represents the amount of drug released in time (t) per unit area A, C shows the initial drug concentration, Cs is the solubility of drug in the matrix media and D represents the diffusivity of the drug molecules in the matrix substance.

3. Result and Discussion

3.1. Preformulation studies

3.1.1. Organoleptic Properties

The Organoleptic properties of gliclazide like colour, odour and taste are reported in **Table 3**.

Table 3: The organoleptic properties of Gliclazide

S. No.	Properties	Outcome
1.	Colour	White
2.	Odour	Odourless
3.	Taste	Metallic taste

3.1.2. Solubility of Gliclazide

Gliclazide is slightly soluble in ethanol [14, 15]. This means that it can dissolve to a reasonable extent in ethanol, making it suitable for formulations or preparations that use ethanol as a solvent. Solubility profile of gliclazide is shown in **Table 4**.

Table 4: Solubility profile of Gliclazide

S. No.	Solvent	Solubility
1.	Water	Insoluble

2.	Methylene chloride	Freely soluble
3.	Acetone	Sparingly soluble
4.	Ethanol	Slightly soluble

3.1.3. Melting point

The melting point of the Gliclazide was found 163 -172 °C.

3.1.4. UV Spectrum

The UV spectrum of Gliclazide is ethanol shown in **Figure 1**. The λmax of GLZ were found to be 216 nm in ethanol. The wavelength of maximum absorbance was considered for further determination of λ_{max} studies.

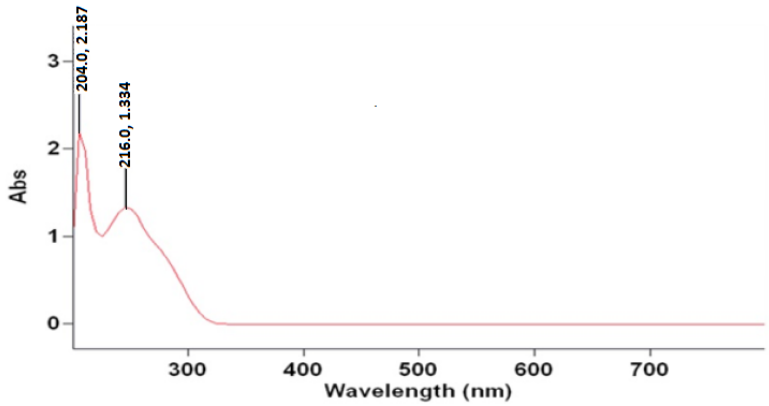

Figure 1: UV absorption spectrum of gliclazide in ethanol

Determination of calibration curves:

The graph of absorption vs. concentration for pure gliclazide was found to be linear in concentration range 0-5 µg/ml at wavelength of maximum absorption shown in **Table 5**. Calibration curves and values of slope, intercept and R2 in ethanol, water and phosphate buffer 7.4 are shown in **Figures 2-4** respectively.

Table 5: Calibration curve values of gliclazide in different solvent

S. No	Solvent	Slope	Intercept	R^2
1.	Ethanol	0.068	0.0095	0.999
2.	Water	0.186	0.0016	0.999
3.	Phosphate buffer 7.4	0.075	0.024	0.999

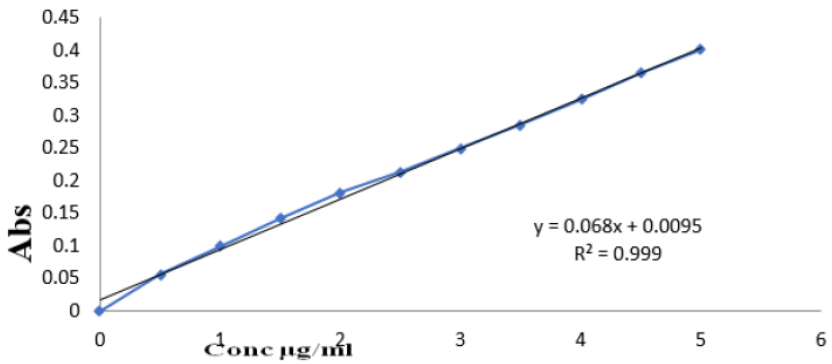

Figure 2: Calibration curve of gliclazide in ethanol

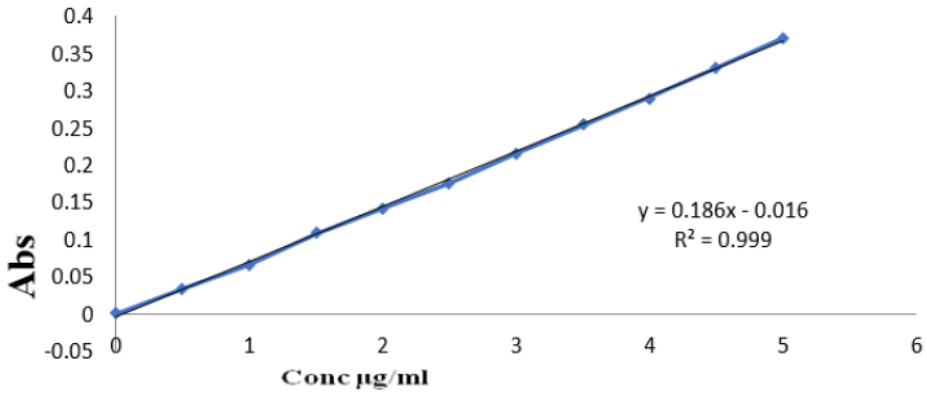

Figure 3: Calibration curve of gliclazide in Water

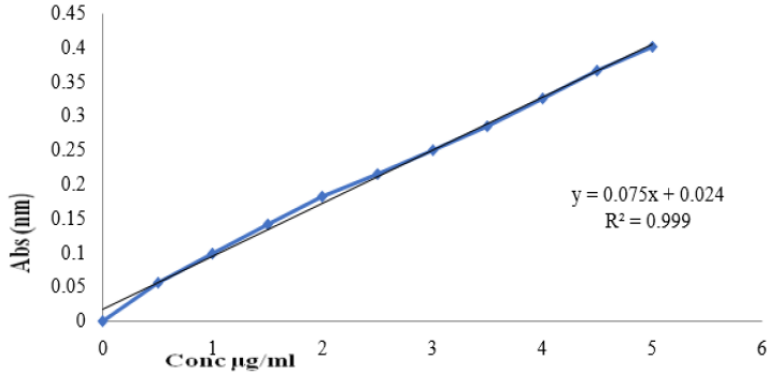

Figure 4: Calibration curve of gliclazide in phosphate buffer 7.4

3.1.5. HPLC Assay of Gliclazide

The drug peak was detected at λ_{max} = 230 nm at room temperature. The retention time of gliclazide was 7.6 mins. The peak appeared well separated, symmetrical, with no fronting or tailing. Linearity was established (r^2 = 0.9998) over concentration range of 25–400 µg/mL. Accuracy was depicted by % GCZ recovery and ranged from 97.50 to 106.80. Inter- and intra-day precision were presented by CV %, which ranged from 0.350 to 0.809. Reproducibility of the calibration curve was performed in 3 different days.

3.1.6. Fourier Transformation Infrared Analysis

An FTIR spectrum of pure Gliclazide is shown in **Figure 5** and different peaks are shown in **Table 6.**

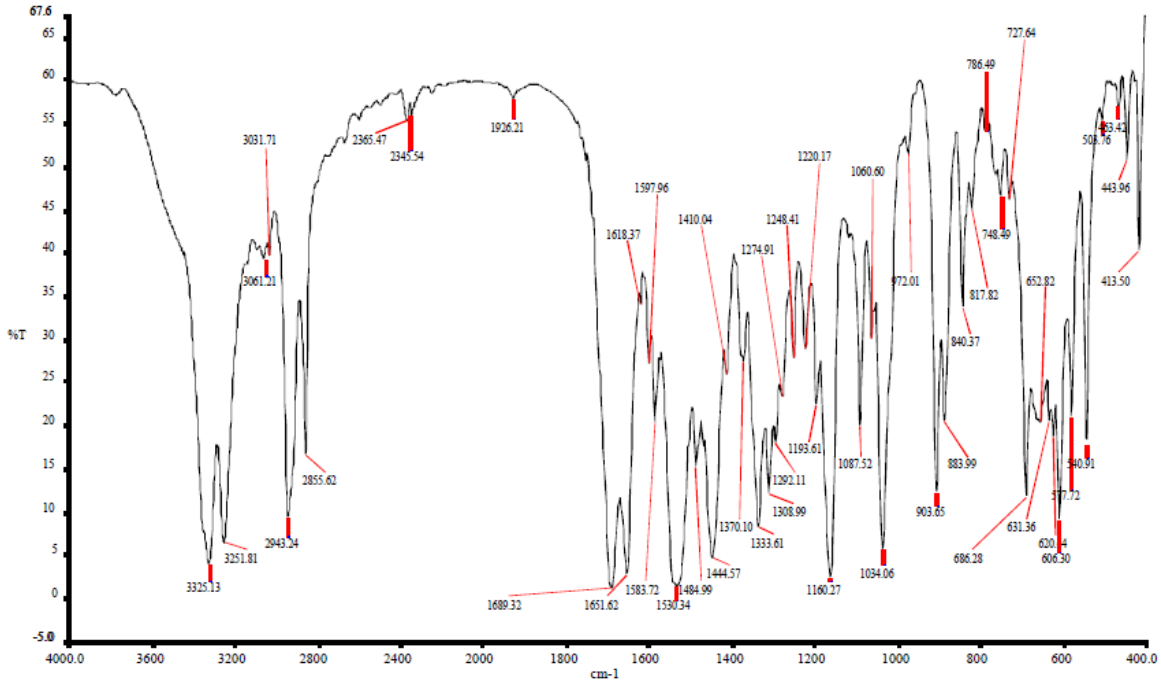

Figure 5: FTIR spectra of pure Gliclazide

Table 6: Interpretation of FTIR Spectra of Gliclazide

Frequency	Vibration mode
1583.72 cm^{-1}	N- H bending
1370.10 cm^{-1}	S=O stretching
3325.13, 3251.81 cm^{-1}	N- H stretching
1689.32 cm^{-1}	C=O stretching
1651.62 cm^{-1}	CONH - stretching

3.2. **Characterization of Gliclazide Loaded PLA Nanoparticles**

(a) Particle Size

The results of mean particle size of gliclazide nanoparticles are shown in **Table 7** and **Figure 6**. Results indicated that particle size was in the range of 295.5 to 720.4 nm. It was observed that with an increase in amount of PLA polymer, particle size also increased because of the hindrance in the breaking of globules due to higher viscosity. On increasing the concentration of surfactant polyvinyl alcohol (PVA), the particle size was found to decrease because surfactant helps to produce new area for the formation of globules and prevents particle aggregation and decreases the size of particles.

Table 7: Particle size of Gliclazide PLA Nanoparticles

Run	Amount of Polymer PLA (mg) X1	Amount of Surfactant PVA (%w/v) X2	Particle Size (nm) Y1
1	100	0.15	580.5
2	150	0.15	720.4
3	100	0.3	510.4
4	150	0.3	620.1
5	100	0.3	463.2

6	150	0.45	566.3
7	100	0.3	473.8
8	100	0.3	450.5
9	50	0.15	410.5
10	50	0.45	295.5
11	50	0.3	398.6
12	100	0.3	498.7
13	100	0.45	376.4

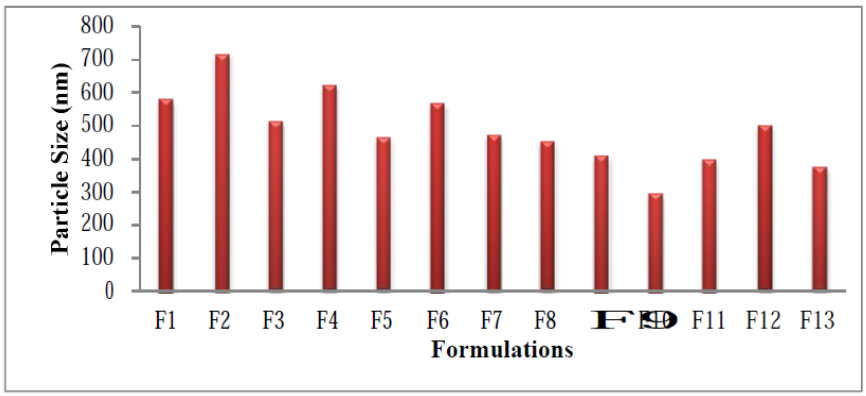

Figure 6: Particle Size of Gliclazide Loaded PLA Nanoparticles of Different Formulations

(b) Percentage Entrapment Efficiency and Percentage Drug Loading

The entrapment efficiency and drug loading of different batches are shown in **Table 8, Figure 7** and **8**. The entrapment efficiency and drug loading were found to be in the range of 50.67 - 79.16% and 14.1 - 36.78% respectively. The entrapment efficiency and drug loading decreased with increase in the amount of PLA polymer which may be due to the more compact polymer coat, which limits drug entrapment and more time taken for the precipitation of polymer which was in higher amount.

The entrapment efficiency and drug loading increased with increase in PVA concentration, this may be due to freer drug available on the surface of nanoparticles.

Table 8: Entrapment Efficiency of Gliclazide PLA Nanoparticles Formulations

Run	Amount of Polymer PLA (mg) X1	Amount of Surfactant PVA (%w/v) X2	Entrapment Efficiency (%) Y2	% Drug Loading Y3
1	100	0.15	62.48	19.13
2	150	0.15	50.67	14.1
3	100	0.3	63.45	21.93
4	150	0.3	52.37	15.9
5	100	0.3	64.02	20.89
6	150	0.45	55.23	17.37
7	100	0.3	63.98	21.4
8	100	0.3	63	20.49
9	50	0.15	64.13	30.14

10	50	0.45	79.16	36.78
11	50	0.3	71.34	32.34
12	100	0.3	65	21.16
13	100	0.45	67.92	25.15

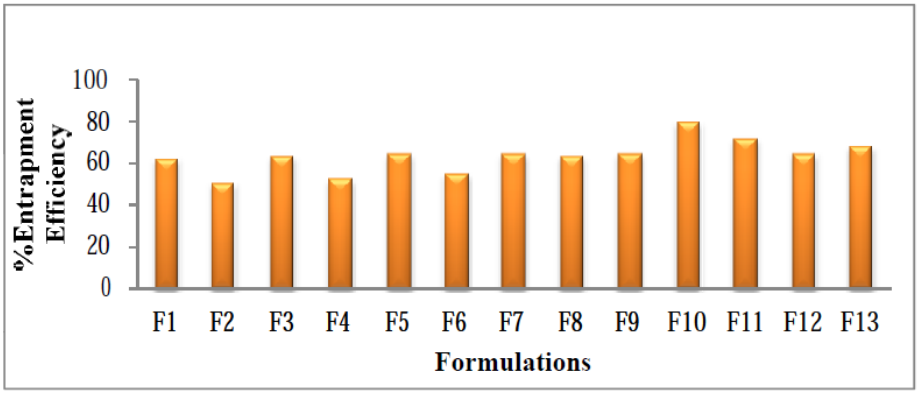

Figure 7: **Entrapment Efficiency of Gliclazide Loaded PLA Nanoparticles of Different Formulations**

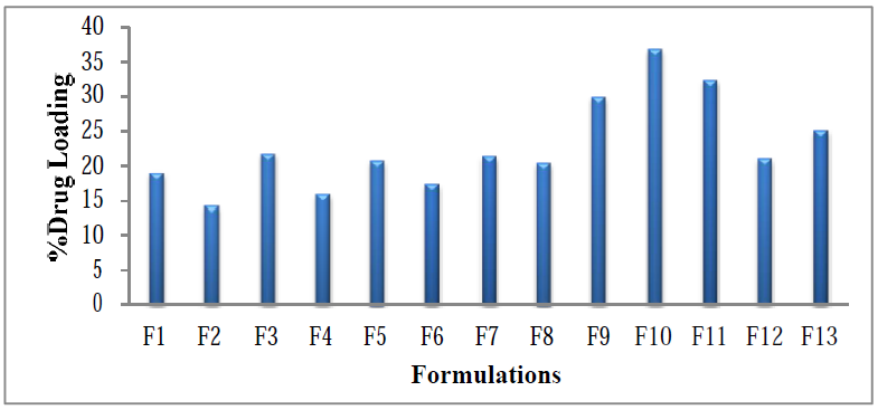

Figure 8: Drug Loading of Gliclazide Loaded PLA Nanoparticles of Different Formulations

3.3. Characterization of Optimized Batch

d) Differential Scanning Calorimetric (DSC)

In **Figure 9** the DSC thermogram of Gliclazide loaded PLA optimized batch is shown. At 207.04°C the DSC thermogram of pure Gliclazide showed a sharp endothermic peak. After nanoparticles precipitation, two peaks are identified. At 169.52°C Formulation shown endothermic peak due to presence of Gliclazide, indicating that there was no interaction between drug and polymer. There was slightly shift in endothermic peak of Gliclazide in drug -loaded nanoparticles as compared to that of pure Gliclazide drug; this may be due to drug being in amorphous form rather than crystalline form.

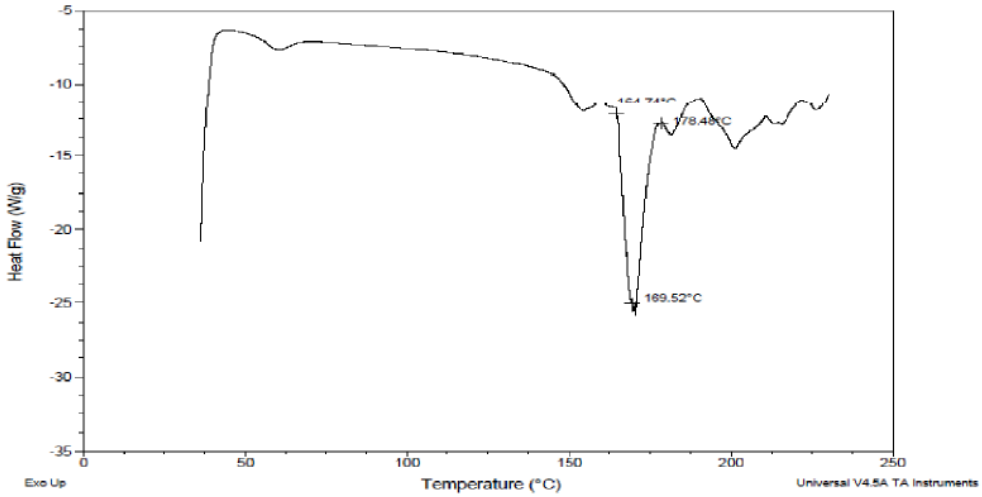

Figure 9: DSC Thermogram of Gliclazide Loaded PLA Optimized Batch

e) Fourier Transformation Infrared (FT-IR) Analysis of Gliclazide PLA nanoparticles

FTIR was used to confirm the incorporation of drug in the nanoparticles. FTIR spectra of drug loaded optimized batch were compared with pure drug and polymers. The FTIR spectrum showed few minor shifting of peaks but no major changes as well as no loss of functional peaks. This indicated the absence of chemical interaction or any changes in chemical composition of drug and other component used during preparation of nanoparticles. FTIR spectra of optimized batch are shown in **Figure 10** and characteristic peak were shown in **Table 9**.

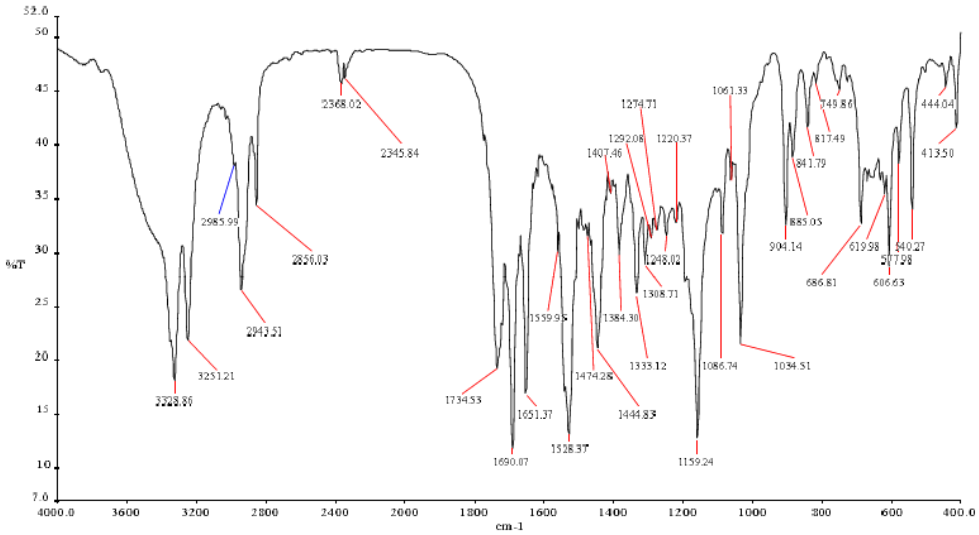

Figure 10: FTIR Spectrum of Gliclazide Loaded PLA Optimized Batch

Table 9: Peak Intensity of FTIR Spectrum of Gliclazide Loaded PLA Optimized Batch

Interpretation	Peaks (cm^{-1}) Observed
N-H bending	1528.37
S=O stretching	1384.30
N- H stretching	3328.86, 3251.21
C=O stretching	1690.07
CONH - stretching	1651.37

C=O stretching of ester group	1734.53

(c) *In-vitro* Drug Release Studies

The percentage cumulative drug release of Gliclazide loaded PLA nanoparticles from all formulations was plotted against time and is shown in **Figure 11** and **12**. The percentage cumulative drug release from the nanoparticles was found to be in the range of 73.72% to 78. 12 % in 10 hrs at pH 6.8. The polymeric nanoparticles displayed a biphasic drug release pattern with initial burst release followed by sustained release pattern. The burst release may be ascribed to the drug associated with the surface of particles. The results displayed that the release was dependent on the amount of polymer and surfactant concentration. An increase in polymer concentration caused a decreased drug release rate due to the high viscosity of PLA. On contact with the dissolution medium, surface of nanoparticles forms viscous gel layers. As the concentration of PLA increased, the viscosity of the gel layers also increased while the diffusion coefficient of drug decreased. However a percentage cumulative drug release increased with increase in surfactant concentration which could be attributed to the decrease in particle size and increase in surface area available for the dissolution.

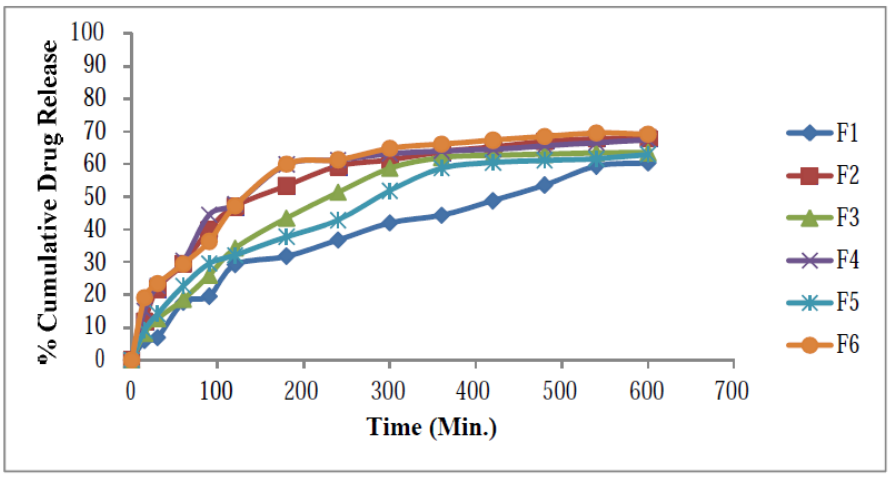

Figure 11: Drug Release Profile of Gliclazide Loaded PLA Nanoparticles of F1-F6 in Phosphate Buffer pH 6.8

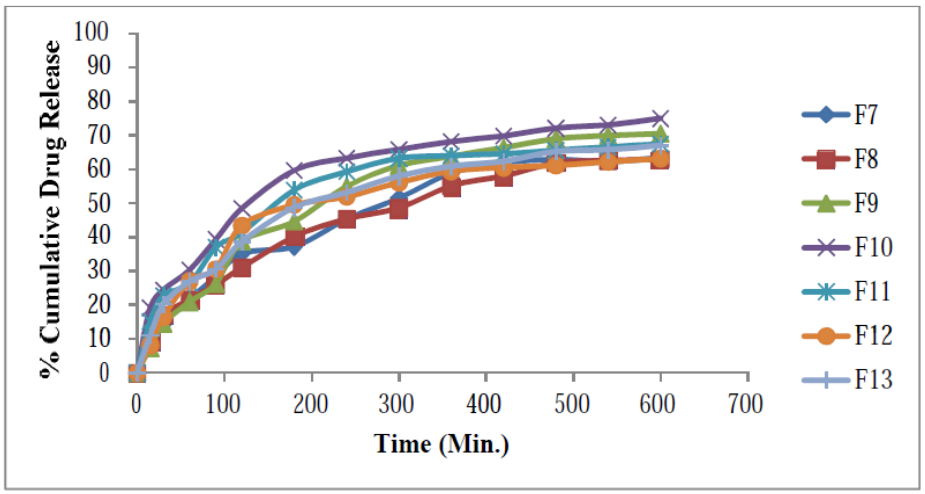

Figure 12: Drug Release Profile of Gliclazide Loaded PLA Nanoparticles of F7-F13 in Phosphate Buffer pH 6.8

(d) **Response Surface Methodology Optimization**

The optimization results of particle size, percentage entrapment efficiency and percentage drug loading are given in the **Table 8**. These responses were individually fitted into various polynomial models. For each response, a suitable model was selected by software on the basis of different parameters such as p value, adjusted R^2, predicted R^2 and predicted residual sum of square (PRESS) value. The model which generated a higher adjusted R^2, predicted R^2 value and low PRESS value was selected as the best fitted model. It was observed that particle size data fitted well in the surface linear model but entrapment efficiency and drug loading showed best fit in to Quadratic model. Each model was validated by ANOVA. The result of ANOVA analysis showed the models to be significant with non significant lack of fit. Surface linear model was found to be significant in case of particle size and Quadratic model was found to be significant for entrapment efficiency and drug loading. Model fit summary of measured responses (particle size, entrapment efficiency and drug loading) is shown in **Table 10**.

The relationship between the formulation variables and the responses in terms of Coded Factors can be represented by the following equations.

Particle Size (Y1) = +489.61 +133.70* A - 78.87 * B

Entrapment Efficiency (Y2) = +64.01 -9.39* A +4.17* B -2.62* AB - 2.45* A^2 + 0.89* B^2

Drug Loading (Y_3) = +21.19 - 8.77* A +2.65* B - 0.84* AB +2.53* A^2 + 0.90* B^2

Where

A = Amount of polymer

B = Amount of surfactant (PVA)

AB = Amount of polymer (PLA) * surfactant (PVA)

Table 10: Model Summary Statistics of PLA Nanoparticles Formulation Responses to Select Suitable Model

Response	Model	Adjusted R^2	Predicted R^2	PRESS	Significance
Y1	Linear	0.9379	0.9080	14031.30	Suggested
	2FI	0.9344	0.8636	20791.59	
	Quadratic	0.9356	0.7599	36599.26	
Y2	Linear	0.9072	0.8133	128.28	
	2FI	0.9500	0.8770	84.47	
	Quadratic	0.9773	0.8960	71.44	Suggested
Y3	Linear	0.9254	0.8721	122.65	
	2FI	0.9242	0.7422	90.12	
	Quadratic	0.9947	0.9874	68.802	Suggested

4. Characterization of Optimized Batch

***In - vitro* Drug Release Profile**

The drug release profile of optimized batch showed that the cumulative drug release was 75.43 % in 10 hrs, in phosphate buffer pH 6.8 (**Figure 13**).

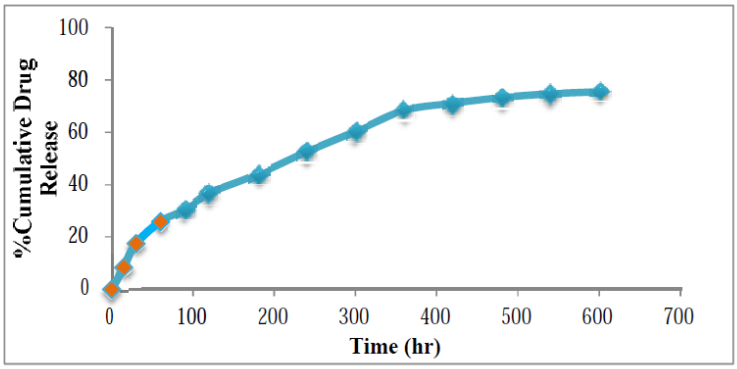

Figure 13: *In- vitro* Drug Release Profile of Gliclazide Loaded PLA Optimized Batch

f) Drug Release Kinetics

The *in-vitro* drug release data of optimized formulation were integral to various kinetic models, which are shown in **Figure 14-16**. The result of optimized formulation was shown in the **Table 11**. The highest R^2 value of optimized PLA nanoparticles was obtained in Higuchi model compared to zero order, first order. Higuchi kinetic model indicated that drug release followed a diffusion mechanism.

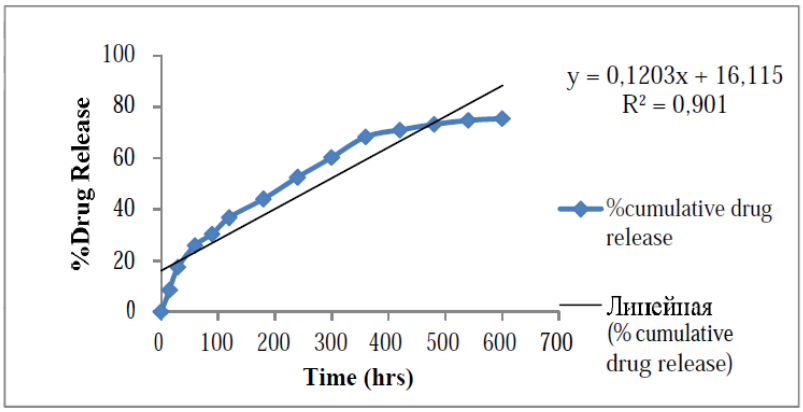

Figure 14: Zero Order Plot of Gliclazide Loaded PLA Optimized Batch

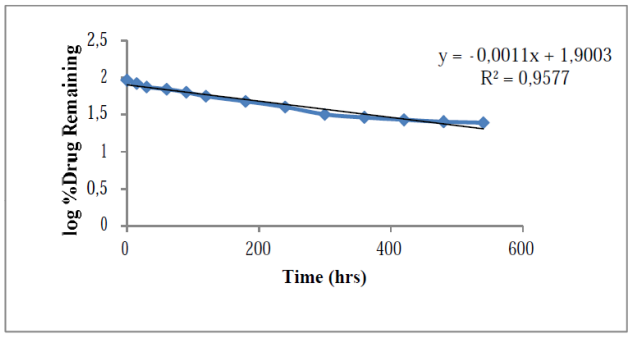

Figure 15: First Order Plot of Gliclazide Loaded PLA Optimized Batch

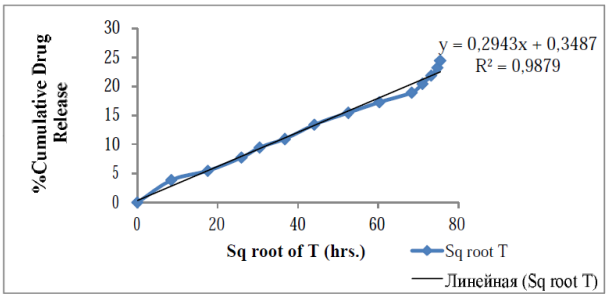

Figure 16: Higuchi Plot of Gliclazide Loaded PLA Optimized Batch

Table 11: Drug Release Kinetics Data Obtained From PLA Polymer Optimized Batch

S. No.	Model	R^2
1.	Zero order	0.900
2.	First order	0.957
3.	Higuchi	0.987
	Best Fit Model Higuchi	

3. Conclusion

The solvent evaporation method was used for preparation of Gliclazide PLA loaded nanoparticles. As the concentration of the PLA increased, particle size also increased but entrapment efficiency and drug loading decreased. However as the concentration of surfactant (PVA) increased, particle size decreased but entrapment efficiency and drug lo adding increased. *In-vitro* drug release studies on Gliclazide loaded polymeric nanoparticles showed and initial burst release which could be due to adsorbed drug on the surface of nanoparticles. This was followed by a slower and sustained release rate from the nanoparticles. The release of the drug from optimized batches of Gliclazide loaded PLA nanoparticles was found to follow the Higuchi model release kinetics.

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