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Design, Fabrication and Characterization of PVA/ PLGA Electrospun Nanofibers Carriers for Improvement of Drug Delivery of Gliclazide in Type-2 Diabetes

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Abstract:
Poor solubility, erratic bioavailability and delivery challenges associated with gliclazide, which is commonly used in type 2 diabetes mellitus (T2DM) treatment, are overcome by exploring electrospun nanofibers technology. Employing emulsion electrospinning method with polyvinyl alcohol (PVA) alone and in combination with poly(D,L-lactide-co-glycolide) (PLGA), nanofibers were fabricated. Different concentrations of PLGA at 0.05, 0.10 and 0.15 %w/v was added to PVA to achieve a modified drug release profile to meet the typical physiological needs of T2DM, such as a faster drug release at meals followed by prolonged release to maintain constant plasma glucose level, is highly desirable in T2DM management. Fabricated gliclazide-nanofibers were characterised by various studies, such as solubility, in-vitro drug release, drug release kinetic, scanning electron microscopy, differential scanning calorimetric, fourier transform infrared spectroscopy. GLZNF2, formulation of Drug: PVA: PLGA 0.1: 10: 0.05 % w/v produced optimized gliclazide nanofibers. The optimized GLZNF2 nanofibers were incorporated into gelatin capsule for oral administration. SEM image of optimized formulation (GLZNF2) shows cylindrical shape fiber indicates gliclazide incorporated homogeneously in polymers with average fiber diameter 4.357±0.83µm. The solubility and dissolution rate of gliclazide nanofibers significantly improved compared to pure gliclazide. The gliclazide nanofibers produce a biphasic drug release profile, initial fast release, followed by prolonged release. Oral fabricated gliclazide fibers have tremendous potential as drug carrier and alternative technology for the improvement of solubility, dissolution rate, reduction in the dosing frequency and better blood glucose control could be explored in T2DM management.

Keywords: electrospun; nanofibers; fabrication; polyvinyl alcohol ; poly(lactic-co-glycolic acid); gliclazide, oral modified drug delivery; type 2 diabetes mellitus

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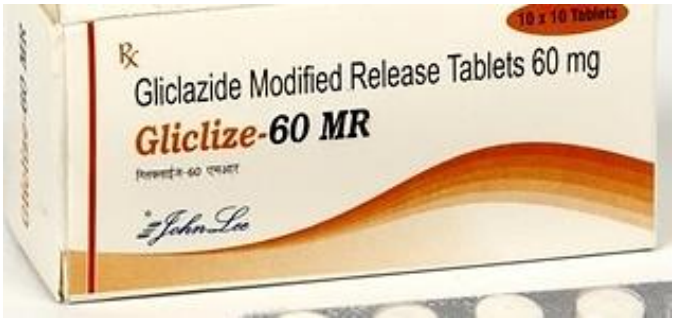
Introduction

Gliclazide

- ✓ **Second generation of sulphonylurea –T2DM**
- ✓ **Low aqueous solubility**
- ✓ **Low dissolution rate**
- ✓ **Variable absorption profile**
- ✓ **BCS class II drug**
  - → low solubility
  - → high permeability
- ✓ **Low Bioavailability,**
- ✓ **Reduce therapeutic efficacy**
  - →**Conventional formulation require multiple dosing**
  - → reduce patient compliance



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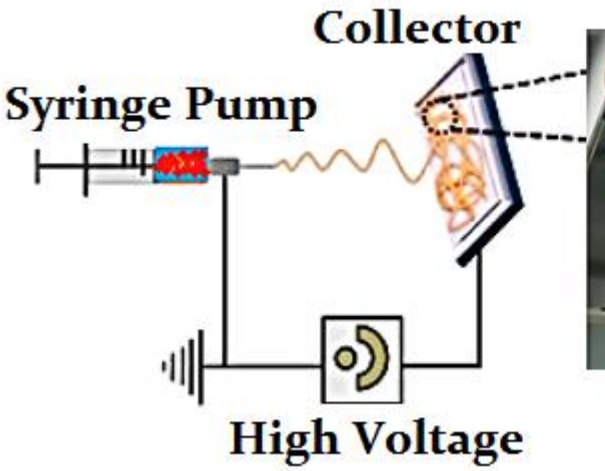
Introduction

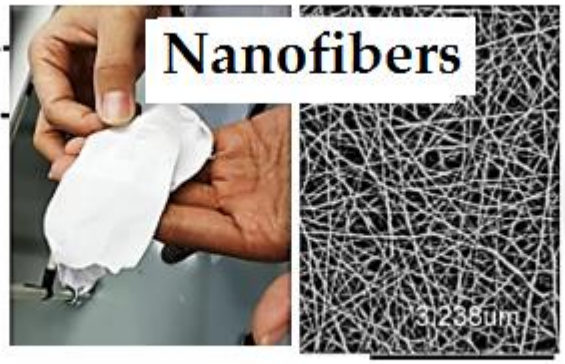
Electrospun method

- **Polymeric electrospun fibers are developed employing polymer solutions under the influence of electrostatic field**
- **Easy operation**
- **Encapsulation efficiency high**
- **Produce large volume nanofiber with various therapeutic agents**

Electrostatic fibers

- **Electrostatic fibers of diameters ranging from nanometers to micrometers**
- **HIGH: surface area, porosity, drug loading capacity**
  - improve solubility of drug
  - modify drug release pattern
- T2DM





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Research objectives

01

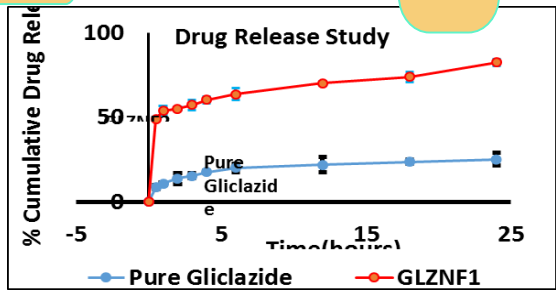
To improve the drug delivery challenges associated with gliclazide in T2DM

02

To develop polymeric nanofiber specialized carrier system for oral delivery of gliclazide

03

To meet the typical physiological needs of T2DM, such as a faster drug release at the time of meals followed by prolonged drug release profile over an extended period



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Experimental: Gliclazide Electrostatic fibers

Emulsion Electrospinning Method

FORMULATION

Gliclazide

Primary polymer:
Polyvinyl alcohol (PVA)

Drug Release modulator:
poly (D, L-lactide-co-glycolide) (PLGA)

PVA and PLGA Combination

FABRICATION PARAMETERS

Metallic needle (inner diameter) in 0.33 mm

Flow rate in 1 ml/h

Ambient condition (Temperature 22 ±1 o C)

Distance between needle's tip and collector in 18 cm

Voltage applied In 19 kV

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Experimental

Formulation Design of Gliclazide Electrostatic fibers

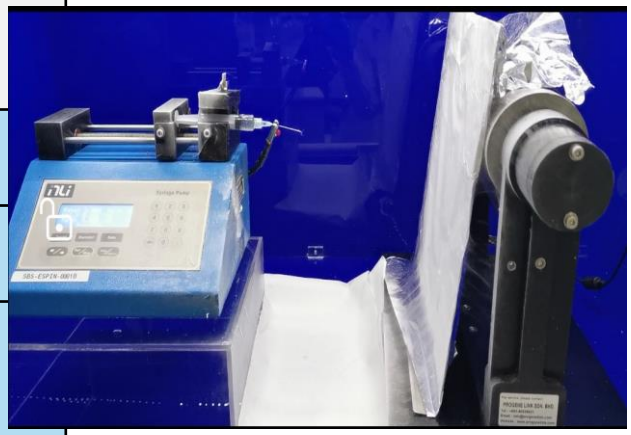
Formulation code	%w/v		
	Gliclazide	PVA	PLGA
BNF0 (BlankPVA Nanofiber)	0	10	0
GLZNF1	0.1	10	0
GLZNF2	0.1	10	0.05
SGNCF3	0.1	10	0.10
GLZNF4	0.1	10	0.15
GLZNF5Caps (GLZNF2 in capsule)	0.1	10	0.05

Electrospinning process - Gliclazide Electrostatic fibers

FABRICATION PARAMETERS

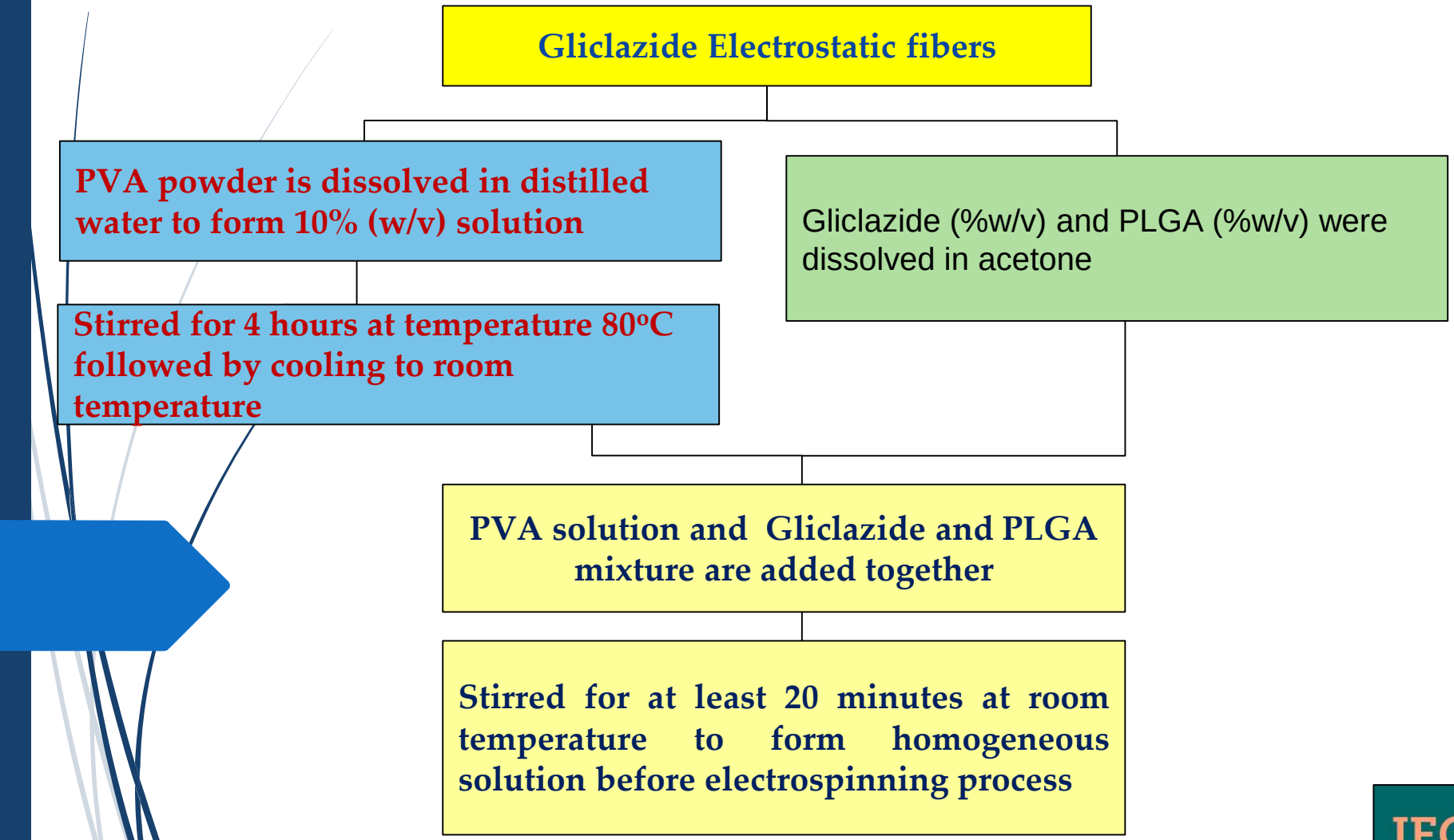
Spinning solution were loaded into 5mL syringe pump

Parameters	Gliclazide Electrostatic fibers
Inner diameter of needle used	0.33mm
Flow rate	1ml/h
Distance between needle's tip and collector	18cm
Voltage applied	19kV



The formed electrospun were then stored in a desiccator contain silica gel .

Preparation of spinning solution - Gliclazide Electrostatic fibers



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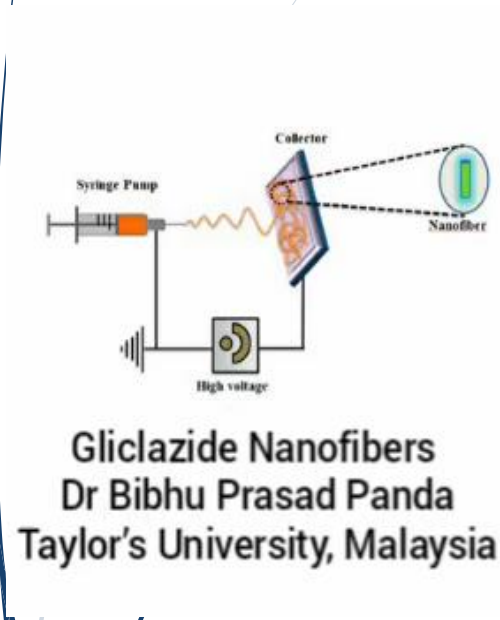
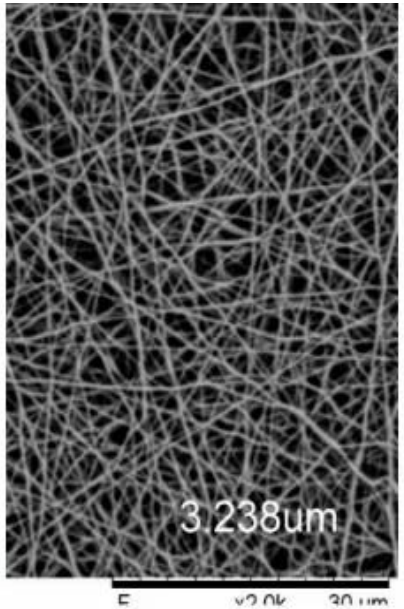
Gliclazide Electrostatic Fibers Manufacturing Video Clips



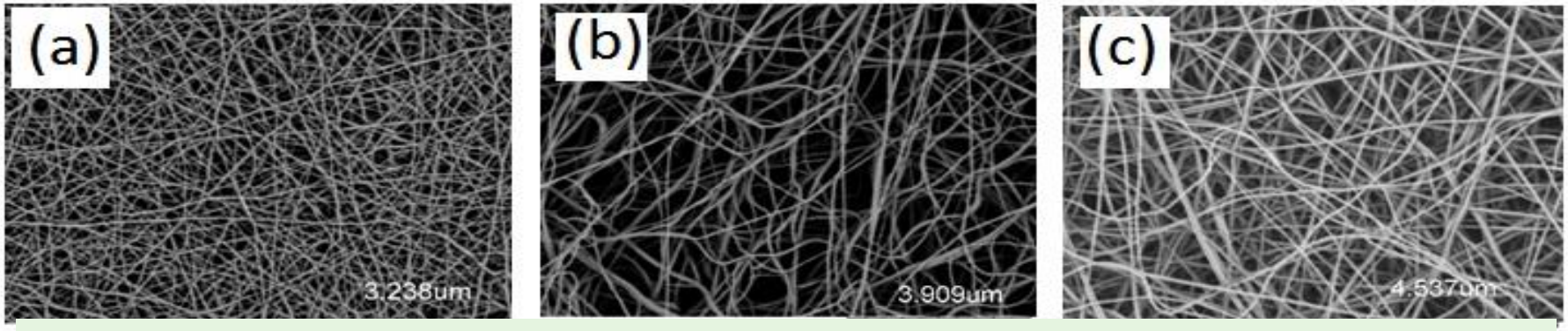


Results and Discussion

Electrospun nanofibers physicochemical characterizations

Formulation code	Drug content (%)	Folds increase in solubility ± SD (Compared with Pure Gliclazide)
BNF0 (Blank PVA Nanofiber)	-	-
GLZNF1	96.82 ± 1.69	4.17 ±.1.04
GLZNF2	98.36 ± 0.87	2.84 ± 1.75
SGNCF3	96.24 ± 2.50	2.25 ± 0.28
GLZNF4	96.13 ± 1.14	1.84 ± 0.17
GLZNF5Caps	97.86 ± 1.36	2.84 ± 1.94

Results and Discussion



Scanning electron microscopy (SEM) images of (a) blank PVA nanofibers, BNF0 formulation , (b) gliclazide nanofibers ,GLZNF1 formulation, and (c) optimised gliclazide nanofibers ,GLZNF2 formulation.

Formulation code	Average fiber diameter ± SD (µm) (From SEM studies)
BNF0 (Blank PVA Nanofiber)	3.238 ± 0.47
GLZNF1	3.909± 1.53
GLZNF2	4.537 ± 1.88
SGNCF3	5.261 ± 1.45
GLZNF4	5.537 ± 2.73
GLZNF5Caps	4.537 ± 1.88

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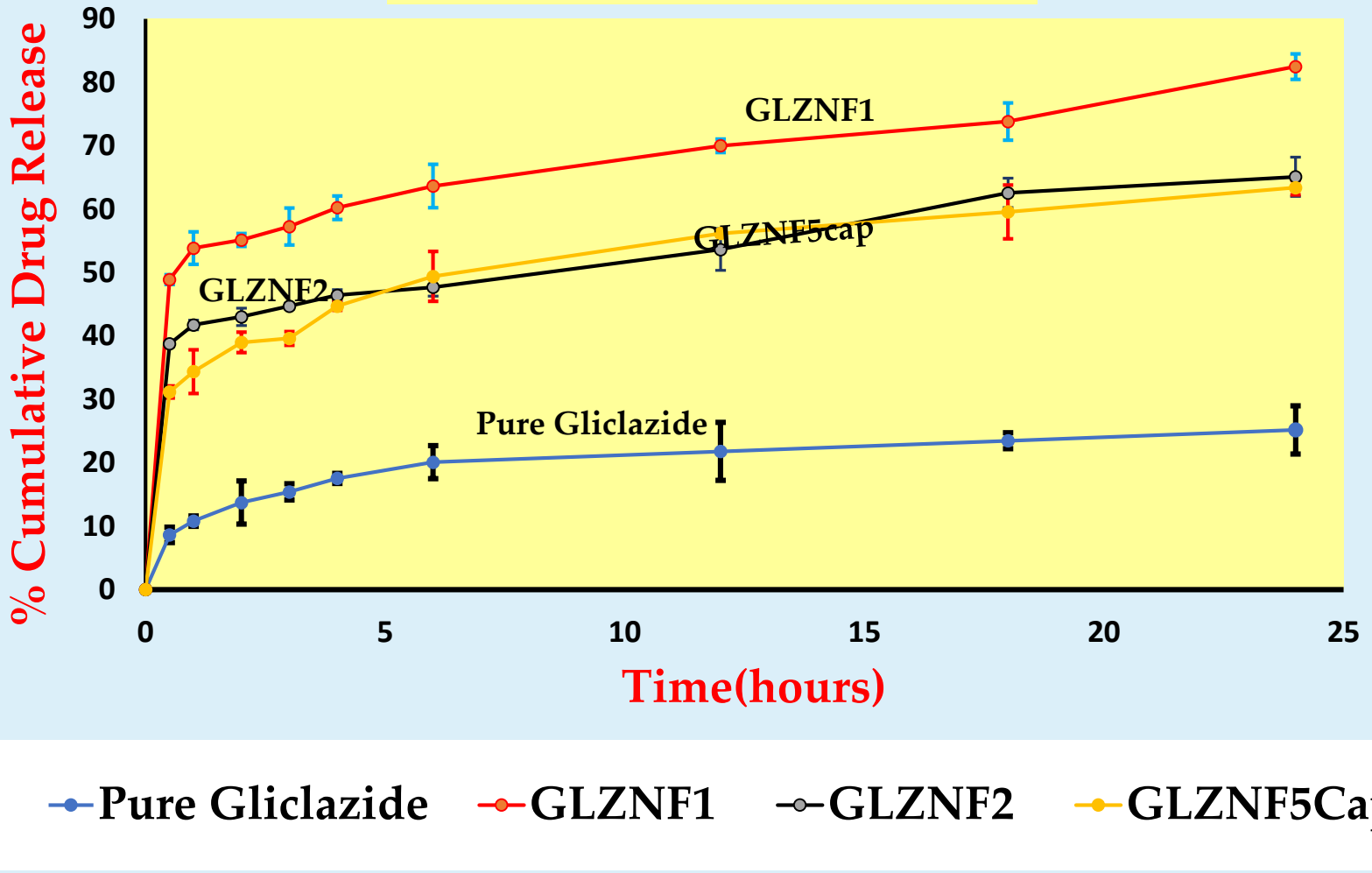
Drug release studies

Time (Hrs)	% Cumulative Drug Release ± SD					
	Pure Gliclazide	GLZNF1 (10%PVA)	GLZNF2 (Optimized Formulation)	GLZNF3	GLZNF4	GLZNF5Cap (Optimized Formulation in capsule)
0.5	**8.62±1.2**	**48.87±0.79**	**38.35±0.49**	**27.306±2.9**	**14.130±0.79**	**31.16±0.94**
1	10.79±0.82	53.84±2.58	41.72±0.75	30.690±1.5	16.254±1.42	34.37±3.45
2	13.714±3.4	55.12±1.02	43.00±1.38	31.968±2.2	17.964±1.74	38.96±1.62
3	15.40±1.3	57.25±2.9	44.69±0.46	34.092±1.4	19.638±0.56	39.6 ± 1.1
4	17.53±0.8	60.22±1.86	46.40±0.9	35.370±2.46	20.934±2.8	44.69±0.67
6	20.08±2.6	63.62±3.43	47.68±1.41	37.908±3.02	22.194±2.41	49.37±3.93
12	21.77±4.57	69.99±1.06	53.62±3.28	41.724±1.98	24.750±0.97	56.16±0.47
18	23.47±1.25	73.81±2.93	62.53±2.32	45.972±2.45	28.152±0.25	59.56±4.24
24	**25.18±3.8**	**82.47±2.01**	**65.08±3.08**	**49.806±2.85**	**31.536±1.47**	**63.37±1.12**

Drug release studies



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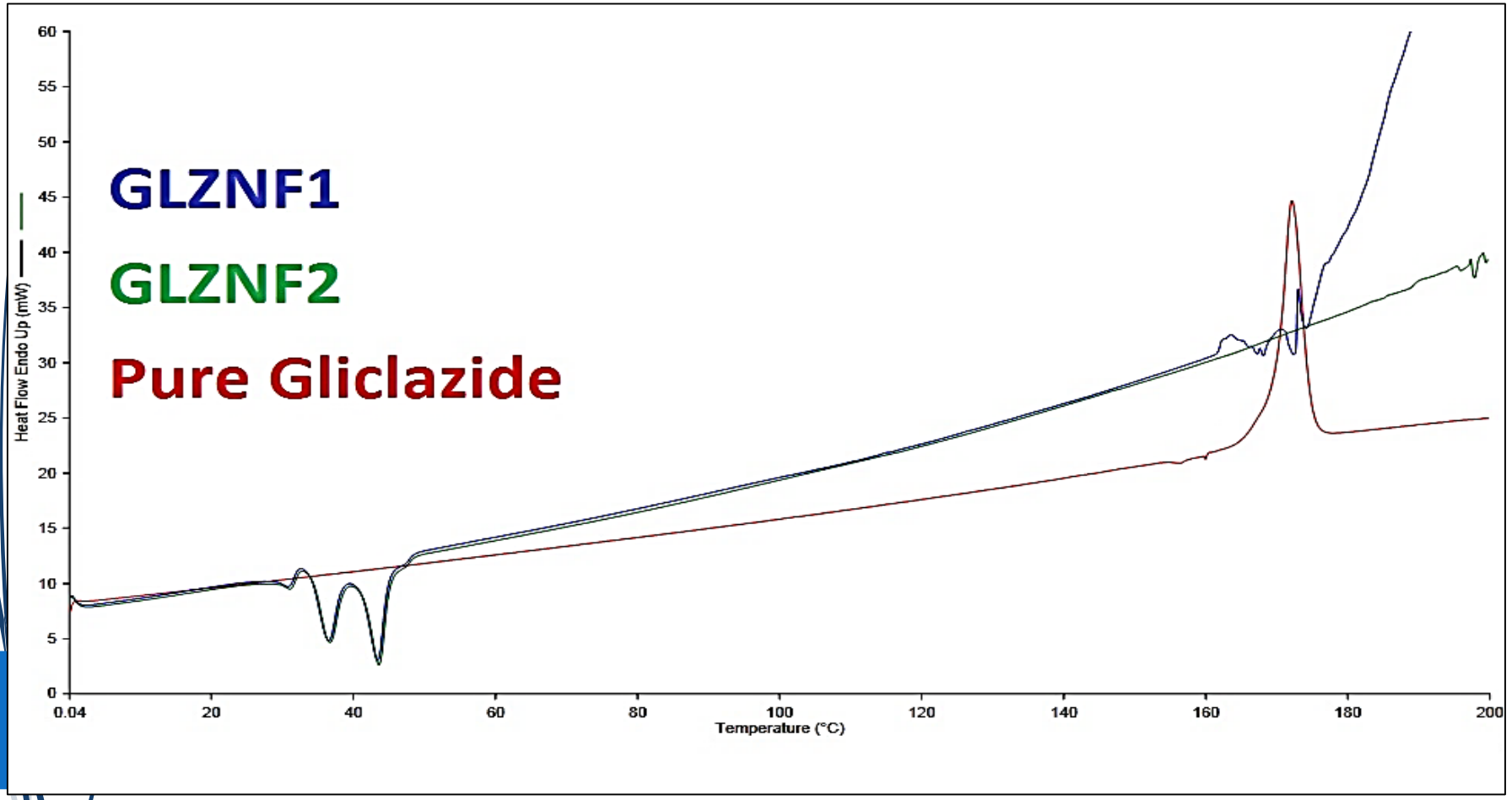
Drug release kinetics studies

Formulation (PVA nanofiber)	Zero-order plots	First-order plots	Higuchi's plots	Korsmeyer-Peppas Plots		
	Correlation coefficient (R_0^2)	Correlation coefficient (R_1^2)	Correlation coefficient (R^2)	Correlation coefficient (Rk^2)	Diffusional exponent (n)	Type of release
GLZNF1	0.478	0.7627	0.712	0.2041	0.453	Fickian diffusion
GLZNF2	0.523	0.7114	0.727	0.2233	0.4498	Fickian diffusion
SGNCF3	0.534	0.6554	0.7681	0.2381	0.4292	Fickian diffusion
GLZNF4	0.5005	0.5499	0.7914	0.2804	0.3938	Fickian diffusion
GLZNF5 Cap	0.5996	0.7586	0.8499	0.266	0.4834	Fickian diffusion

Differential scanning calorimeter (DSC) studies



- Pure gliclazide : sharp endothermic peak at 172.13 ºC
- GLZNF2 , GLZNF1: No sharp melting peak of gliclazide.
- Indicates :Gliclazide highly dispersed in the electrospun polymeric nanofibers and converted to an amorphous state during the process of electrospinning.

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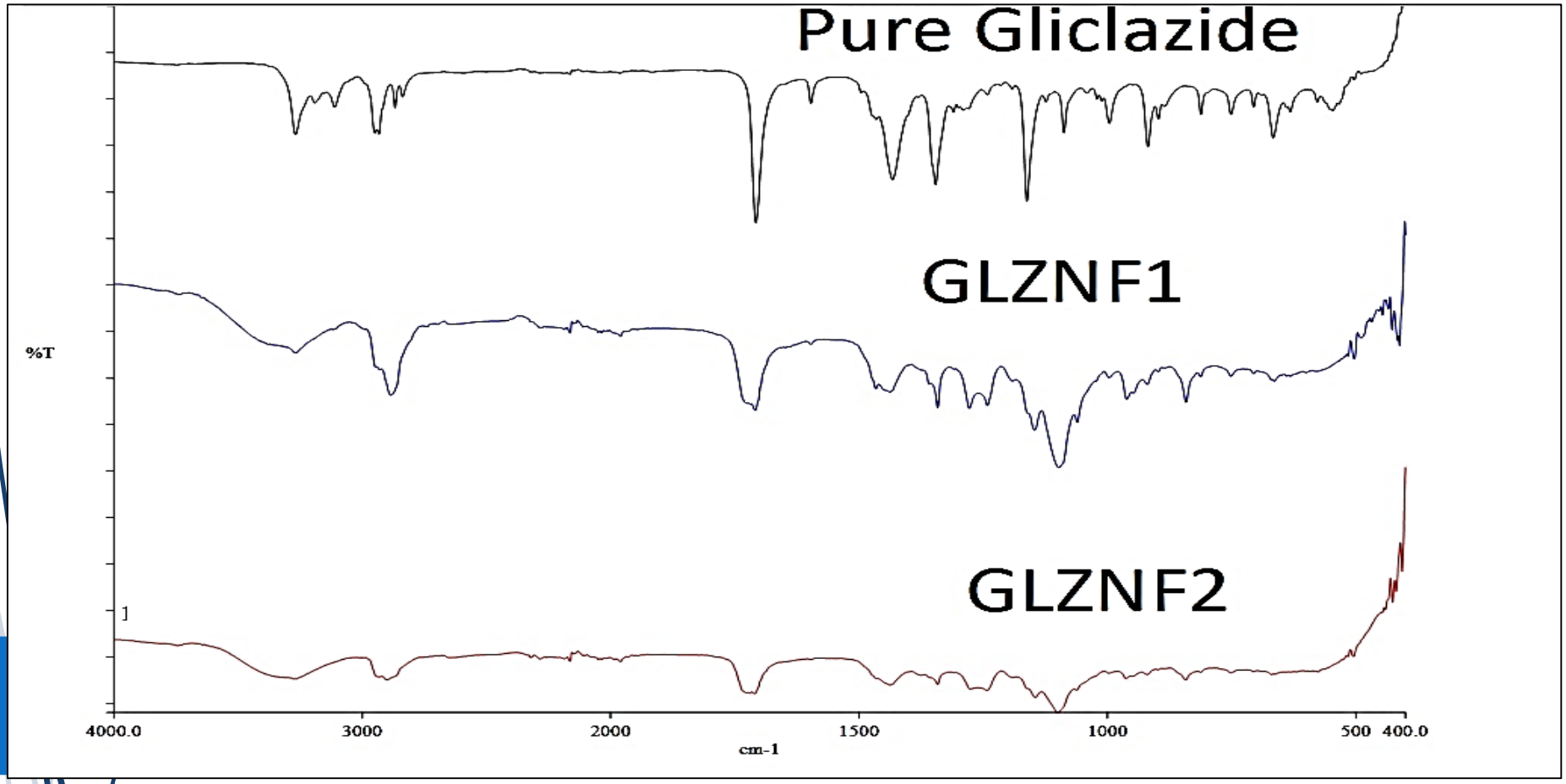
Fourier transform infrared spectroscopy studies



All these gliclazide characteristic peaks were observed in gliclazide nanofiber formulations.

Fingerprint region of formulated nanofiber sharp peaks were significantly decreased, or some disappeared: indicate the formation of amorphous composites.

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Conclusions

- The purpose of this study to fabricate drug-loaded fibres and establish a proof of concept for the electrospun method of making electrostatic fiber as a functional specialised carrier system for oral delivery of gliclazide in type 2 diabetes mellitus (T2DM), was successfully achieved.
- The optimized formulation of gliclazide nanofibers composed of with Drug: PVA: PLGA in 0.1: 10: 0.05 % w/v ratio successfully overcome the drug delivery challenges associated with gliclazide.
- The optimized formulation of gliclazide nanofibers was successfully incorporated into an empty gelatin capsule for oral administration.
- The SEM image of optimized gliclazide nanofibers formulation shows the cylindrical shape of fiber indicates gliclazide was incorporated homogeneously in the polymer.

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Conclusions

- This study also highlights optimized gliclazide nanofibers formulation, successfully achieved a modified drug release to meet the typical physiological needs of T2DM, such as a faster drug release at the time of meals followed by prolonged drug release profile over an extended period to maintain constant plasma glucose level, is highly desirable in T2DM management.

- Overall findings of the study suggest, oral fabricated gliclazide fibers have tremendous potential as drug carrier and alternative technology for the improvement of solubility, dissolution rate, reduction in the dosing frequency and better blood glucose control could be explored in T2DM management.

Thank You!

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