Formulation Development and Evaluation for Nanofibrous Tablet of Glibenclamide

Kalamkar Tanmayi [1*], Veer Vikram[2], Dr. Kasabe Amit[3], Patil Dipti[1], Gavhane Mayuri[1]

[1]Research Scholar, Department of Pharmaceutical Quality Assurance, PDEAs Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Pune, Maharashtra, India.

[2]Assistant Professor, Department of Pharmaceutical Quality Assurance, PDEA'S Shankarrao Ursal College of Pharmaceutical Sciences & Research Centre, Kharadi, Pune, Maharashtra, India.

[3]Assistant Professor, Department of Pharmaceutical Quality Assurance, PDEA'S Shankarrao Ursal College of Pharmaceutical Sciences & Research Centre, Kharadi, Pune, Maharashtra, India.

For Correspondence –Kalamkar Tanmayi Dattatray

kalamkartanu@gmail.com

ABSTRACT - Poor solubility, erratic bioavailability and delivery challenges associated with Glibenclamide, which is commonly used in type 2 diabetes mellitus (T2DM) treatment, are overcome by exploring electrospun nanofibers technology. Employing electrospinning method with polyvinyl alcohol (PVA) combination with poly(D,L-lactide-co-glycolic acid) (PLGA), nanofibers were fabricated. Different concentrations of PLGA at 0.02%, 0.03% and 0.05% w/v were 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, which is highly desirable in T2DM management. Fabricated Glibenclamide-nanofibers were characterized by Scanning electron microscopy (SEM) and Fourier transform infrared (FTIR) spectroscopy. Fabricated nanofibers compressed with other excipients in a tablet and used for oral administration. Formulated tablets were evaluated for hardness, friability, thickness, drug content and in-vitro study. F3 batch was selected as optimize batch from the similarity factor, cumulative drug release and drug content study.

KEYWORDS – Nanofibers, Electrospinning, Glibenclamide, Fabrication

INTRODUCTION - **Nanofibers** are fibers with diameters in the nanometer range (typically, between 1 nm and 1 μm). Nanofibers can be generated from different Polymers and hence have different physical properties and application potentials. Examples of natural polymers include collagen, cellulose, silk fibroin, keratin, gelatin and polysaccharides such as chitosan and alginate. Examples of synthetic polymers include poly (lactic acid) (PLA), polycaprolactone (PCL), polyurethane (PU), poly(lactic-co-glycolic acid) (PLGA), poly (3-hydroxybutyrate-co-3-hydroxyvalerate)

(PHBV), and poly(ethylene-co-vinyl acetate) (PEVA). Polymer chains are connected via covalent bonds. The diameters of nanofibers depend on the type of polymer used and the method of production. All polymer nanofibers are unique for their large surface area-to-volume ratio, high porosity, appreciable mechanical strength, and flexibility in functionalization compared to their microfiber counterparts. [1]

Diabetes mellitus Type 2 is a long term metabolic disorder that is characterized by high blood sugar, insulin resistance and relative lack of insulin. It primarily occurs due to obesity. Symptoms of high blood sugar include frequent urination, increased thirst and increased hunger [2]. Type 2 diabetes is a progressive condition in which the body becomes resistant to the normal effects of insulin and/or gradually loses the capacity to produce enough insulin in the pancreas. We do not know what causes type 2 diabetes. Type 2 diabetes is associated with modifiable lifestyle risk factors. Type 2 diabetes also has strong genetic and family related risk factors. Type 2 diabetes is diagnosed when the pancreas does not produce enough insulin (reduced insulin production) and/or the insulin does not work effectively and/or the cells of the body do not respond to insulin effectively known as insulin resistance. [3] Over 90% cases of diabetes are type 2. [4,5] Glibenclamide, also known as glyburide, is an antidiabetic drug belonging to the class of sulfonylureas. Therapy with Glibenclamide is usually initiated with 2.5mg given once daily. The maximal recommended daily dose is 20mg. Glibenclamide is 200 times more potent than tolbutamide in evoking pancreatic secretion of insulin. It differs from other oral hypoglycemic drugs where in tolerance to this action apparently does not occur. It also upregulates insulin receptors in the periphery, which seems to be the primary action. It has a special status in the treatment of non-insulin-dependent diabetes mellitus because it is effective in many cases which are resistant to all other oral hypoglycemic drugs. It differs from other oral hypoglycemic drugs i.e. more effective during eating than during fasting [6].

The present study was conducted to design and evaluate Glibenclamide nanofibrous tablet for increasing Half life of Glibenclamide by formulating nanofibrous tablet which will be prolonging the duration of action as antidiabetic medicine.

MATERIALS AND METHODS :

MATERIAL : Glibenclamide was obtained as a sample product from Yarrow chemical products, Mumbai. PLGA and PVA was obtained from Solanki Enterprises, Pune. HPMC K4M and cross-linked PVP was obtained from Ashland Netherlands. Co., Magnesium Stearate, Microcrystalline cellulose, Talc was obtained from Research Lab Fine chem. Industries, Mumbai.

METHOD :

Preparation of Spinning Solution for Glibenclamide Nanofibers

Polymer PVA was dissolved in distilled water to form 10% (w/v) PVA solution. The polymeric PVA mixture was then stirred for 4 h at a temperature of 80 °C followed by cooling at room temperature. Then, Glibenclamide, 0.1% *w/v* and PLGA in different concentration 0.02%, 0.03%, 0.05%, were pre-dissolved in 1 mL of acetone and added in to PVA polymer solution. The mixture was then stirred for at least 20 min at room temperature to form homogenous solution before performing the electrospinning

process. The design of different batches of formulations and their compositions used in the preparation of the spinning solution for Glibenclamide loaded PVA/PLGA electrospun nanofibers.[7]

Electrospinning method for Solutions

All spinning solutions were prepared at room temperature under stirring for 24 h to ensure their homogeneity. Electrospinning was conducted using a γ-High Voltage Research DC power supply generator with a maximum voltage of 50 kV. The electrospinning solutions were fed through the tip of the needle by syringe pump with a stable flow rate (0.5 mL/h). Meanwhile, high voltage (15 kV) was applied to the needle and the nanofibers were concurrently collected on the grounded and steady metal plate which was placed at 15 cm from the needle and covered with Al foil. Temperature and relative humidity were 20±2°C and 60±5%, respectively.

Characterization of Glibenclamide Nanofibers :

Scanning Electron Microscopy :

The morphology of Glibenclamide + PVA + PLGA Nanofibers formulation were observed using a tabletop scanning electron microscope (Hitachi TM3000) with 20 kV. The metal carriers of copper stubs with double-sided conductive tape were used to fix the electrospun nanofibers samples. Before an examination, a thin layer of gold was coated on the sample using an ion sputtering device. The diameter of fibers from the SEM image was measured using ImageJ software. Different parts of each nanofiber sample was selected for measurement and the average fiber diameter was calculated. [8]

Preparation of Nanofibrous tablet of Glibenclamide by Direct Compression Method

Nanofibrous tablet of Glibenclamide are prepared by direct compression method. The corresponding amount of nanofibers and excipients were accurately weighed and mixed properly and the matrix is formed. The tablet blends for different batches (F1-F3) are prepared according to table and further studied for Pre-compression properties.

Table 1: Formulation of Nanofibrous tablet of Glibenclamide

Sr. No.	Ingredients	Formulation Codes		
		F1(mg)	F2(mg)	F3(mg)
01	Glibenclamide Nanofibers	10	10	10
02	HPMC K4M	10	20	30

03	Cross-linked PVP	50	50	50
04	Microcrystalline Cellulose	164	154	144
05	Magnesium Stearate	8	8	8
05	Talc	8	8	8
Total		**250**	**250**	**250**

PRECOMPRESSION EVALUATION OF BLEND OF SUSTAINED RELEASE TABLET OF GLIBENCLAMIDE [9,10,11,12,13,14,15,16] :

Angle of Repose

This is the maximum angle possible between the height of pile of blend powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the coefficient friction (Ɵ) between the particles. Hence the rougher and more irregular the surface of particles the greater will be angle of repose.

$$\Theta = \tan^{-1} (r/h)$$

Where, H = height of the pile

Table 2 : Standards for Angle of Repose

Angle of Repose	Flowability
<20	Excellent
20-30	Good
30-34	Passable
>40	Very Poor

Bulk density:

Apparent bulk density (BD) was determined by pouring blend into a graduated cylinder. Weighted quantity of the powder mass (M) was poured into measuring cylinder, then the powder was levelled carefully, and the unsettled apparent volume Vo was noted to the nearest graduated unit. The bulk density was calculated in gm/ml by the formula: The bulk density was calculated using the formula

Bulk Density = M/Vo

Tapped density:

After determination of the bulk density, the cylinder was tapped mechanically by mounting on a holder in a mechanical tapped density tester that provided a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and the tapped volume Vt was measured to the nearest graduated unit. The tapping was repeated foran additional 750 times and the tapped volume was measured. Final tapped volume was measured and tapped density was calculated by the formula:

Tapped Density = M/Vt.

Compressibility Index and Hausner's Ratio:

The Compressibility Index and Hausner's Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generallyless significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index or Carr's index (CI) and the Hausner's ratio (HR) which is calculated using the following formulas

Compressibility Index

The simplest way for measurement of free flow of powder is compressibility, a indication of the case with which a material can be induced to how is given by compressibility index (CI) which is calculated as follows

Carr's Index = [(Tapped density - Bulk density)/ Tapped density] ×100

Table 3: Standards for Compressibility Index

Carr's Index	Properties
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
35-38	Very Poor
>40	Very Very Poor

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner's ratio (Hr) = [Tapped Density (ρtap)/Bulk Density (ρb)]

Table 4: Standards for Hausner's Ratio

Hausner's ratio	Flow
1.2-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.5-1.6	Poor

MANUFACTURING OF NANOFIBROUS TABLET OF GLIBENCLAMIDE BY DIRECT COMPRESSION METHOD

Accurate quantity of Glibenclamide nanofibers and all ingredients were weighed according to formula powders except talc and magnesium stearate was blended homogeneously in mortar and pestle for 15 minutes. Prepared powder blend was passed through sieve no. 60. Finally, Talc and Magnesium stearate passed from sieve no. 30 added and was further mixed for10 minutes.

Accurately weighed 250 mg homogeneously mixed powder blend was fed manually and compressed with constant compression force and hardness on 16 stations tablet compression machine with 9 mm, breakthrough, and flat faced punches.

Total three formulations were prepared.

EVALUATION OF NANOFIBROUS TABLET OF GLIBENCLAMIDE [9,11,13]

The prepared tablet batches (F1-F3) are subjected to post compression evaluation and evaluation parameters like appearance, weight variation, thickness, hardness, friability, content uniformity, disintegration time, dissolution time was performed and the results are shown in **table 10**.

Appearance:

The tablets were visually observed for capping, chipping and lamination.

Weight Variation:

When a tablet is designed to contain a certain quantity of medication in a specific amount of tablet formula, the weight of the tablet is frequently tested to confirm that the correct amount of drug is included in the tablet. In actuality, ten tablets were consumed and weighed on a digital weighing balance individually. The averageweight of the tablets was determined, and the weight of each tablet was compared to the average. If no more than two tablets are outside the % restriction and no tablet varies by more than twice the percentage limit, the tablet passes the test.

Table 5: Specifications of % weight variation allowed in tablets

Average Weight of Tablet	% Deviation Allowed
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250or more	5

Thickness:

The uniformity of tablet size is dependent on the thickness of the tablet. Vernier caliper was used to determine thickness. randomly selected three pills from each formulation were tested to determine it.

Hardness:

The "force necessary to shatter a tablet in diametric compression test" is the definition of hardness. As a result, tablet crushing strength is also known as hardness. The resistance before use is determined by the hardness of the material. For each formulation the hardness of 6 tablets was determined using a Pfizer hardness tester. In the hardness tester, tablet was held along its oblong axis in between the two jaws of the tester and the

load necessary to crush it was measured. Then force was applied until the tablet fractured. The value at this point was noted in kg/cm2.

Friability:

This test is used to determine if tablets can survive abrasion while being packed, handled, or transported. Friability is a sign of inadequate tablet ingredientcohesiveness. Friability of the tablets was determined using Roche Friabilator. A total of ten pills are weighed and placed in the Friabilator, which is made up of a circular plastic chamber separated into two or three compartments. The chamber rotates at 25 revolutions per minute for 4 minutes, dropping the tablets 15 cm away and completing100 rotations. The pills are then weighed for the second time. The weight difference isobserved and given as a percentage difference. It's best if it's less than 1%.

% Friability = (W1-W2)/W1 X 100

Where,

W1 = Weight of tablet before test

W2 = Weight of tablet after test

Content uniformity

The Glibenclamide content was estimated as follows :

20 tablets were finely powdered and weight equivalent to 10 mg of Glibenclamide was dissolved in 100 ml of 0.1N HCL and assayed against 0.1 N HCL for drug content using UV-Visible spectrophotometer at 229 nm.

Disintegration test:

Six tablets were placed in each six tubes of the basket and the apparatus operated containing water maintained at 37^0C as the disintegration fluid. The Disintegration time was recorded.

In-vitro Dissolution studies

Dissolution profiles of Glibenclamide tablets were determined using the USP Type II Dissolution test apparatus (paddle) (Electrolab, Mumbai, India). set with a paddle speed of 50 rpm & at temperature 37° C ± 0.5°C. The dissolution media used were 900 mL of 0.1N HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 12 h. 5 ml samples wereremoved at specified intervals up to 1h and filtered through Whatmann filter paper. An equal volume of fresh medium, prewarmed at 37^0C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout

the test. Samples were analyzed by UV spectrophotometer at 274 nm. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

Stability Study

The prepared sustained release tablet of Glibenclamide were placed in plastic tubes containing desiccant and stored at ambient conditions, such as room temperature at 40^0C ± 2^0C /75 % RH ± 5% for period of 90 days. Each tablet is weighed and wrapped in aluminum foil and packed in black PVC bottle and put at above specified condition in a heating humidity chamber for 3 months and evaluated for their physical appearance, hardness, disintegrate time, dissolution testing and drug content at specified intervals of time.

RESULTS AND DISCUSSION

Spectrophotometric Analysis of Glibenclamide UV Spectrophotometric Analysis

Determination of λ max of Glibenclamide in 0.1 N HCL

In UV spectroscopy study, the maximum wavelength (λ max) of Glibenclamide in 0.1N HCL was found to be 229 nm. The reported λ max value of Glibenclamide in 0.1N HCL was also 230 nm, so the values similar with the reported value indicates that the given sample of Glibenclamide was in pure form.

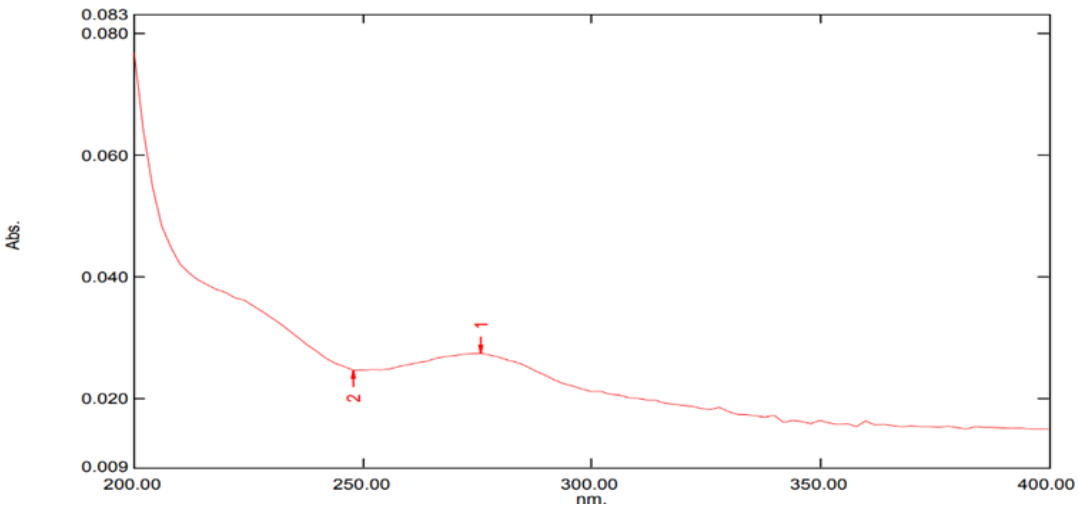

Figure 1: UV Spectrum of Glibenclamide in 0.1 N HCl at 229 nm

Preparation of Standard Calibration Curve of Glibenclamide in 0.1N HCl

The Standard curve of Glibenclamide was determined by plotting absorbance Vs concentration at 229 nm. It was found that there was linear relationship between concentration and absorbance with R^2 value 0.9988. Which reveals that, the drug Glibenclamide obeys the Beers lamberts law.

Table 6: UV Absorbance of Glibenclamide in 0.1 N HCl at 229 nm

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.028
3	20	0.057
4	30	0.087
5	40	0.121
6	50	0.14

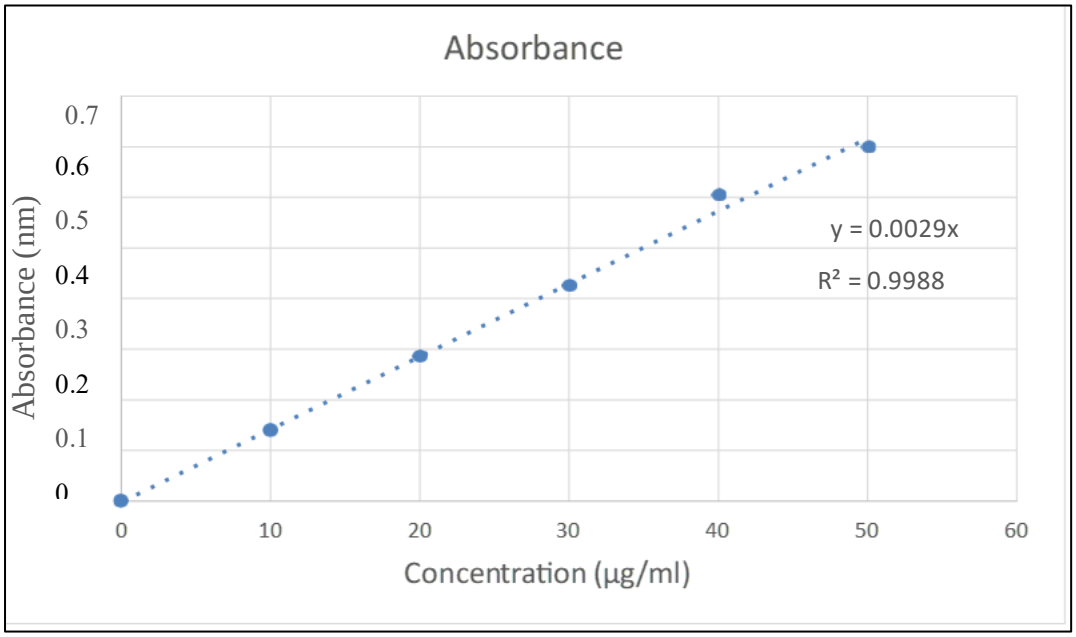

Figure 2: Standard Calibration Curve Graph of Glibenclamide in 0.1N HCL

Determination of λ max of Glibenclamide in 6.8 Phosphate Buffer

In UV spectroscopy study, the maximum wavelength (λ max) of Glibenclamide in 6.8 PhosphateBuffer was found to be 229 nm. The reported λ max value of Glibenclamide in 6.8 Phosphate Buffer was also 230 nm, so the values similar with the reported value indicates that the given sample of Glibenclamide was in pure form.

Sr. no.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.12
3	20	0.215
4	30	0.315
5	40	0.4
6	50	0.48
7	60	0.6

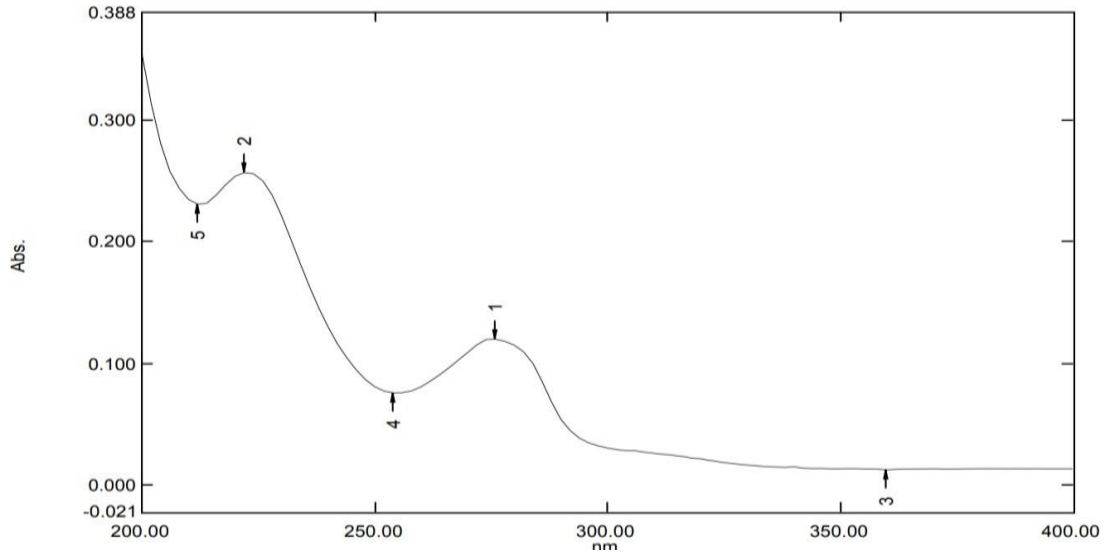

Figure 3: UV Spectrum of Glibenclamide in 6.8 Phosphate Buffer at 229 nm

Preparation of Standard Calibration Curve of Glibenclamide in 6.8 Phosphate Buffer: The Standard curve of Glibenclamide was determined by plotting absorbance Vs concentration at 229 nm. It was found that there was linear relationship between concentration and absorbance with R2 value 0.9986. Which reveals that, the drug Glibenclamide obeys the Beers lamberts law.

Table 7: UV Absorbance of Glibenclamide in 6.8 Phosphate Buffer at 229 nm

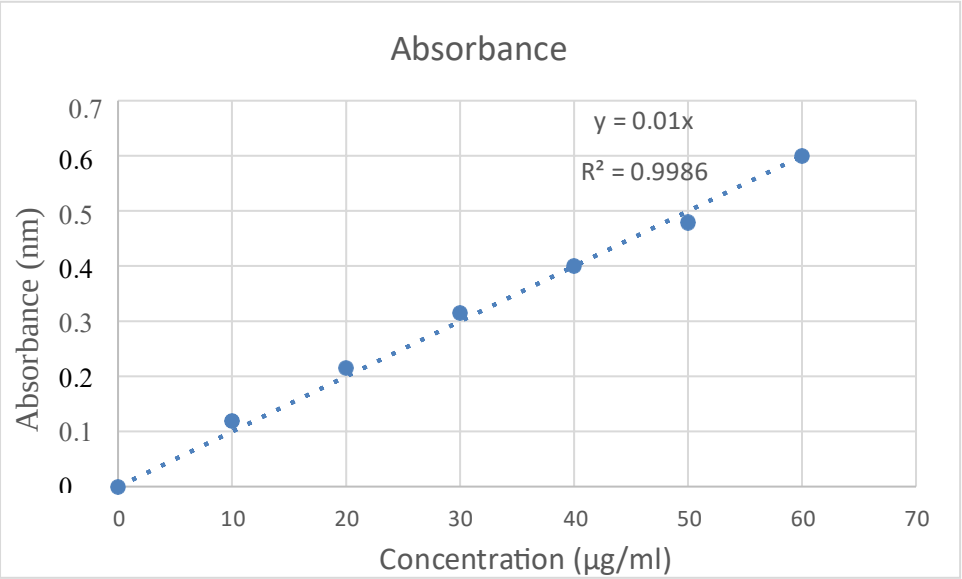

Figure 4: Standard Calibration Curve Graph of Glibenclamide in 6.8 Phosphate Buffer

Drug-Excipient Compatibility Study

Fourier Transform Infra-red Spectroscopy (FTIR) Interpretation of Glibenclamide

The FTIR spectrums of pure Glibenclamide and physical mixtures of drugs and polymers were studied separately as per the excipients used in the formulation. It was observed that there were no major shifts in the main peaks of either drug. This indicates that there were no compatibility problems with the drug with the polymers and excipients used in the formulation. Glibenclamide had peaks at 1658 (C=O amide), 2890 (C=H), 3471 (NH stretch), 1033 (S=O), 1072 (C-O-C).

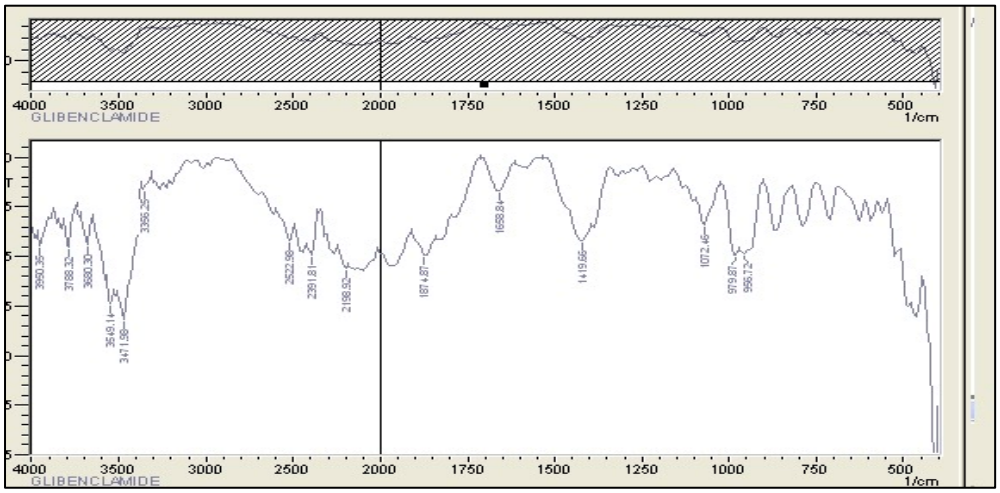

Figure 5: FTIR Spectrum of Glibenclamide

Fourier Transform Infra-red Spectroscopy (FTIR) Interpretation of FTIR of Glibenclamide Nanofibers + HPMC (K4M) + Cross-linked PVP + Microcrystalline Cellulose + Magnesium Stearate + Talc

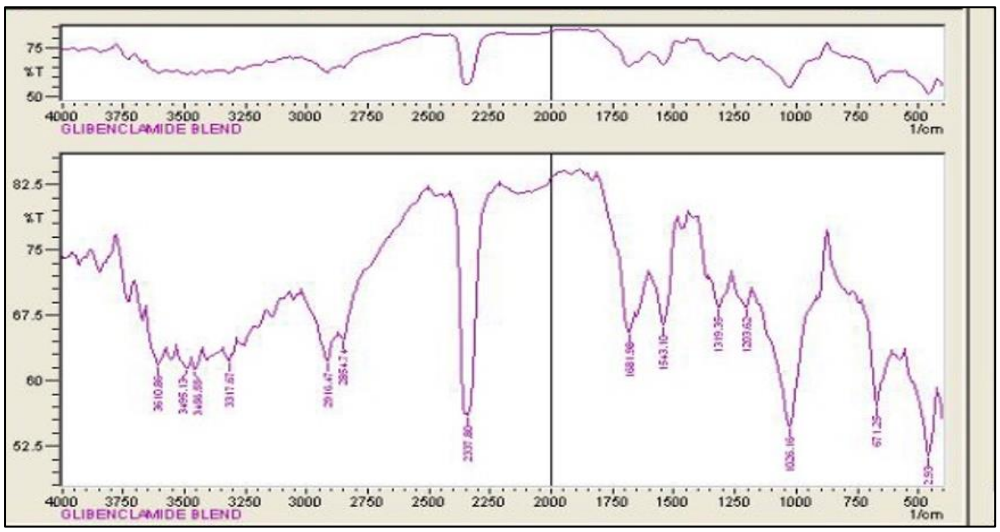

Figure 6 : FTIR Spectrum of Glibenclamide Nanofibers + HPMC (K4M) + Cross-linked PVP + Microcrystalline Cellulose + Magnesium Stearate + Talc

Characterization of Glibenclamide Nanofibers

Scanning Electron Microscopy :

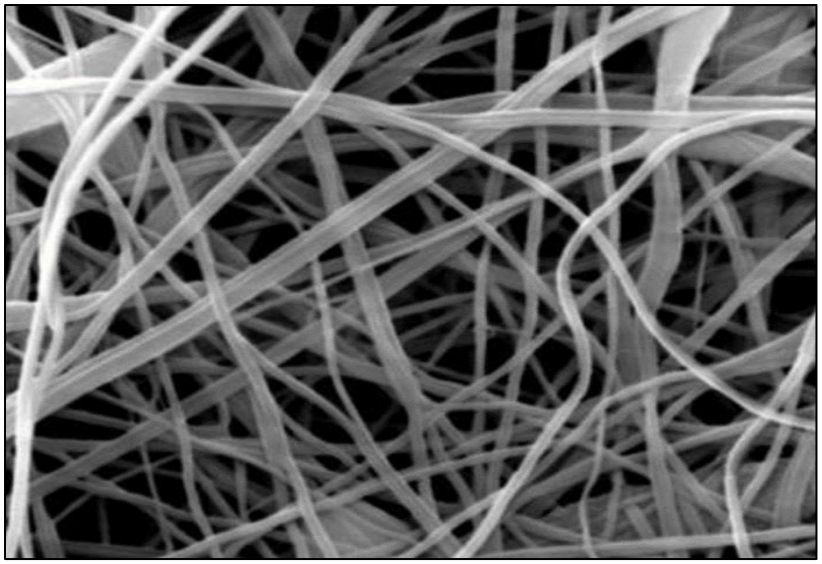

Figure 7: SEM image of batch first Nanofibers

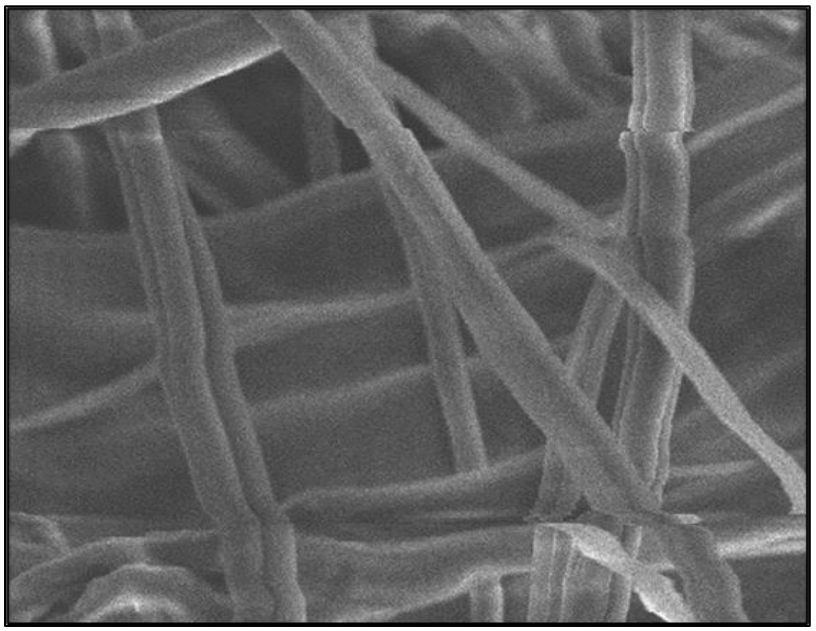

Figure 8: SEM image of batch second Nanofibers

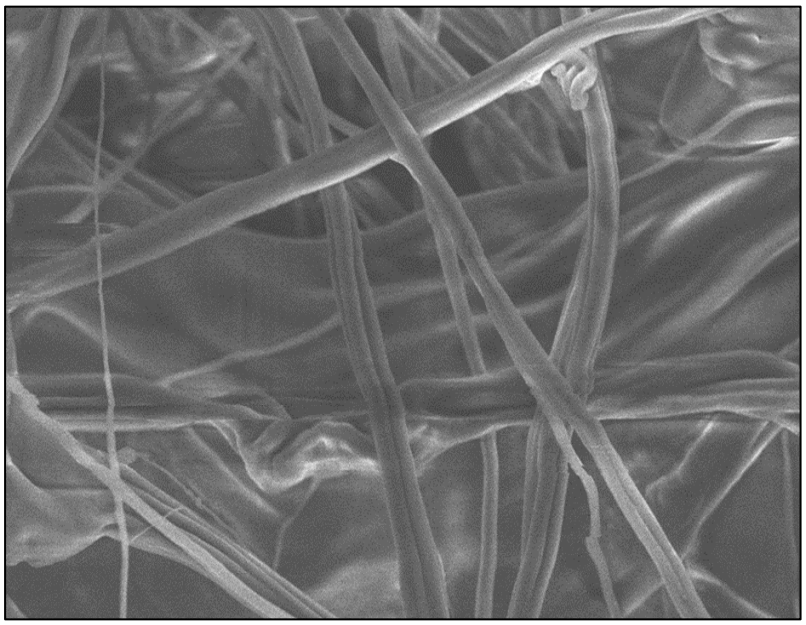

Figure 9: SEM image of batch second Nanofibers

Table 8 :The effect of electrospinning parameters on the size of the nanofibers

Effect of flow rate		**Effect of distance**		**Effect of Volt**	
Flow rate (mL h−1)	**Size (nm)**	**Distance (cm)**	**Size (nm)**	**Voltage (kV)**	**Size (nm)**
0.3	**213±**	**5**	**125±108**	**10**	**547±115**
0.5	**174±**	**10**	**653±156**	**20**	**326±123**
0.7	**452±**	**15**	**221±253**	**30**	**452±147**
0.9	**369±**	**20**	**198±45**	**50**	**251±125**

PRECOMPRESSION EVALUATION OF BLEND OF NANOFIBROUS TABLET OF GLIBENCLAMIDE:

Sustained release tablets of Glibenclamide were prepared by direct compression method using polymer HPMC-Calcium phosphate compex. A total of five formulations were designed. The flow properties of the powder mixture are important for the uniformity of mass of the tablets; the flow of the powder mixture was analysed before compression to tablets. Low Hausner`s ratio (≤1.18), compressibility index (≤15.68) and angle of repose (≤ 29.39) values indicated fairly good flowability of the powder mixture **Table 9.**

Table 9: Precompression Evaluation of tablet for sustained release tablets

Formulations	Angle of repose (Θ^o)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's Ratio (H_R)	Carr's Compressibility index (%)
F1	27.68±0.5	0.37±0.20	0.41± 0.32	1.10±0.10	9.75±0.71
F2	28.21±0.9	0.38±0.02	0.45±0.02	1.18±0.11	15.55±0.5
F3	28.41±0.3	0.36±0.35	0.42±0.62	1.16±0.21	14.29±0.80

Results are mean of three dimensions*

EVALUATION OF SUSTAINED RELEASE TABLET OF GLIBENCLAMIDE:

As the tablet powder mixture was free flowing, tablets produced were of uniform weight with acceptable weight variation in the range from 298 mg to 301 mg due to uniform die fill. Hardness (5.7 ± 0.5 – 6.1 ± 0.3 kg/cm2) and friability loss (0.71 ± 0.04 - 0.82 ± 0.03 %) indicated that tablets had good mechanical resistance. Drug content was found to be high (≥ 98.75 %) in all the tablet formulations **Table 10.**

Table 10: Evaluation of Sustained Release Tablet of Glibenclamide

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)
F1	248±0.50	3.45±0.25	5.7± 0.5	0.73±0.04	98.75±0.45
F2	251±0.58	3.55±0.10	5.9± 0.2	0.76±0.07	98.23±0.04
F3	249±0.20	3.48±0.17	6.0± 0.3	0.82±0.03	99.67±0.37

***In vitro* % Drug Release of Drug from Tablet**

All the three tablet batches Nanofibrous tablet of Glibenclamide were subjected for the in vitro dissolution studies using tablet dissolution test apparatus (USP type II). The dissolution media used were 900 mL of 0.1 N HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 12 h.

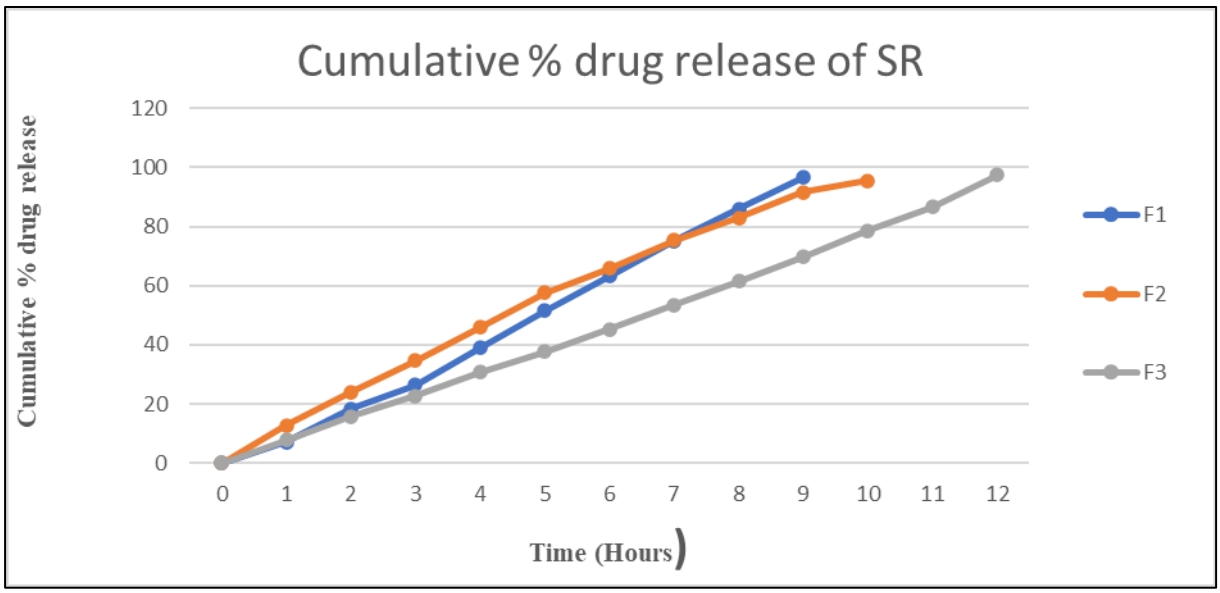

Figure 10 : Cumulative % drug release of Nanofibrous tablet

STABILITY STUDY

The formulation F3 was selected for stability studies on the basis of their high cumulative % drug release time was studied. The stability studies were carried out at 40˚C±2˚C/75˚C±5% relative humidity for the selected formulation up to two months. For every 1-month time interval the tablets were analysed for drug hardness, content uniformity, % drug release up to two months.

CONCLUSION

The purpose of this study was to fabricate drug-loaded fibers and establish a proof of concept for the electrospun method of making electrostatic fiber as a functional specialized carrier system for oral delivery of Glibenclamide in type 2 diabetes mellitus (T2DM). The drug delivery challenges associated with oral Glibenclamide delivery are poor solubility, low dissolution rate, variable gastrointestinal absorption and erratic bioavailability. In this research, Glibenclamide loaded PVA/PLGA electrostatic fibers were successfully fabricated to improve the drug delivery challenges with enhanced drug dissolution and modified drug release profile employing the electrospinning method. The formulation composed of with Drug :PVA : PLGA in 0.1:10:0.05% w/v ratio produced optimized and desired Glibenclamide nanofibers. Formulated nanofibers were evaluated for Scanning Electron Microscopy (SEM) study. Then formulation of Glibenclamide loaded nanofibers was compressed into an tablet for oral administration. Formulated tablets were evaluated for hardness, friability, thickness, drug content and in-vitro study. F3 batch was selected as optimize batch from the similarity factor, cumulative drug release and drug content study.

ACKNOWLEDGEMENT

For the completion of the research work the authors would like to show sincere gratitude to PDEA'S Shankarrao Ursal College of Pharmaceutical Sciences & Research Center, Kharadi, Pune to provide a lot of support and help whenever needed.

CONFLICT OF INTEREST

All authors declared no conflicts of interest

REFERENCES-

1. http://en.m.wikipedia.org/wiki/.Nanofiber
2. *https://en.wikipedia.org/wiki/diabetes_mellitus*
3. *https://www.diabetesaustralia.com.au/type-2-diabetes*
4. Tripathi K.D, Essential's of Pharmacology 7th edition, Page. No.258.
5. Anitha P., Ramkanth S., Salem T.S., Umasankari S., Reddy B.P. and Chetty M., Pak. J. Pharm. Sci., 2011; 24(2): 155-163.
6. *Marikanti Rajkumar et.al. J.Chem.Pharm.Res.,2010,2(4):291-303*
7. Ghafoor, B.; Aleem, A.; Najabat Ali, M.; Mir, M. Review of the fabrication techniques and applications of polymeric electrospun nanofibers for drug delivery systems. J. Drug Deliv. Sci. Technol. 2018, 48, 82–87, doi:10.1016/j.jddst.2018.09.005.
8. Baishya, H. Application of Mathematical Models in Drug Release Kinetics of Carbidopa and Levodopa ER Tablets. J. Dev. Drugs 2017, 6, 1–8, doi:10.4172/2329-6631.1000171.
9. Lieberman H.A., Lachman L., The Theory and Practice of Industrial Pharmacy, Indian Edition, CBS Publishers, and Distributors Pvt. Ltd., 2009, 293, 457, 479-501.
10. Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms: Tablets, Ed 3, New York, Marcel Dekker, 1990.225-228.
11. https://go.drugbank.com/drugs/DB01016
12. Michael E Aulton. Pharmaceutics, The Science of Dosage form Design. 2nd Edition. 2005.335-346.
13. Leon Lachman, Herbart liebeman. The theory and practice of industrial pharmacy. Indian Edition CBS publishers.2009.331-334.
14. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. “Tutorial Pharmacy”. New Delhi, India: CBS Publishers and Distributors; 1986: 211-233.
15. 5. Shah D, Shah Y, Rampradhan M. Drug Dev.Ind. Pharm. 1997; 23(6): 567-574.
16. 6. Wells J., Pharmaceutical Preformulation: The Physicochemical Properties Of Drug Substances In: Aulton ME, “Pharmaceutics: The Science of Dosage Form Design”. International eds: Churchill Livingstone; second Eds.2002; 133-134.
17. Indian Pharmacopoeia, Controller Of Publications, Govt. Of India, New Delhi, Fourth Edition, 1996; Vol-II: 736.