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FORMULATION AND PREPARATION OF TRANSDERMAL PATCHES OF GLIMIPRIDE PART -2

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ABSTRACT: Transdermal drug delivery has been accepted as a potential non-invasive route of drug administration, with advantages of prolonged therapeutic action, less side effect, easy use and improved patient compliance. Glimepiride is an anti-diabetic drug with a shorter half life of ~5 h, low bioavailability and extensive first pass metabolism due to these limitations required to maintain the therapeutic level it has chosen as transdermal drug delivery system. To formulate and evaluate transdermal drug delivery system of Glimepiride using polymers such as tristerin, soya lecithin and Eudragit RS100 by solvent casting technique. Formulation of transdermal patches of glimipride and optimization of SLN transdermal patches. Central composite design (CCD) was applied by using design-expert to optimize composition of tristerin and soya lecithin for transdermal drug delivery. Prepared drug loaded SLNs were evaluated for particle size analysis, DSC, Drug entrapment efficiency, SEM and *in-vitro* release studies. The present study of formulation and preparation of transdermal patches of Glimipride to provide better efficiency of drug other dosage form.

Keywords: Transdermal patches, Transdermal drug delivery, Glimepiride, Solvent casting method, Central composite design, Anti- diabetic patches

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INTRODUCTION: Nowadays about 74% of drugs are taken orally and are found not to be as valuable as most wanted. To advance such characters transdermal drug delivery system was emerged. With the creation of current time of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) recognized itself as an important part of novel drug delivery systems.

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Recent advances in nanoparticulate systems for improved drug delivery display a great potential for the administration of wide variety of active pharmaceuticals. The transdermal route in particular is an attractive candidate for the steady and sustained delivery of insulin into the blood.

Although the stratum corneum poses a significant barrier for protein absorption, once the protein passes through this barrier, the transdermal route offers several unique advantages. Firstly, proteo-lytic degradation of drug is low because the skin contains relatively few proteases. Secondly, painless, noninvasive, and patient-friendly application of patches offers good patient compliance. Thirdly, patches are also easy to remove in the event of

hyperinsulinemia [1, 2, 3, 4]. The purpose of the present work was to develop transdermal formulation of Glimepiride which increases the patient compliance and enhance the bioavailability by using polymers and permeation enhancers.

MATERIALS AND METHODS:

Materials: Glimepiride was a gift sample from USV Limited, Khed, Ratnagiri, Maharashtra, India. Tristearin was purchased from TCI Pvt. Ltd., India. Soya lecithin was obtained as gift sample from A. B. Enterprises, Mumbai, India. Tween 80 are obtained from S.D. Fine chemical limited, Bangalore.

Glassware: Various glassware are used such as pipette, micropipette, measuring cylinder, petridish, beaker, funnel, sampling vials, volumetric flask and Hamilton syringe *etc*.

Instruments: Various types are used such as UV Double beam spectrophotometer, HPLC, Magnetic stirrer, Digital weighing balance, Melting point detector and Hot air oven *etc*.

Optimization of Solid Lipid Nanoparticles Formulation: There are various formulations variables which affect the preparation and properties of solid lipid nanoparticles. Which were identified and studied. These formulations variables can be categorized as follows. Drug concentration; lipid concentration, surfactant concentration and process variables *i.e.* stirring speed, stirring time and sonication time. The optimization was done on the basis of particle size, polydispersity index and drug loading efficiency.

A. Optimization of Glimepiride variables.

a. Optimization of Lipid/Lecithin ratio

b. Optimization of Drug/Lipid ratio

c. Optimization of Surfactant concentration

B. Optimization of process variables

1. Optimization of Stirring speed

2. Optimization of Stirring time

3. Optimization of Sonication Time

C. Optimized parameters

A. Optimization of Formulation Variables:

Optimization of Lipid / Lecithin Ratio: For optimization of lipids ratio, the SLN formulation were prepared with varying ratio of two lipids *i.e.* tristearin and soya lecithin in the following ratio (like 1:0.5, 1:1, 1:1.5, 1.2% w/w) keeping other parameters constant **Table 1** and **Fig. 2**. Optimization was drawn on the basis of average particle size and polydispersity index (PDI) of SLNs which was determined using Malvern Zetasizer.

Optimization of Drug / Lipid Ratio: For optimization of drug/lipids ratio, the SLN formulation F2 was selected and different SLN formulation were prepared in different ratio gives in following **Table 2** in % w/w of drug and lipid (tristearin and soya lecithin) keeping all other parameters constant. Optimization was drawn on the bases of average particles size of SLN and % drug entrapment. The drug entrapment efficiency was determined by centrifugation.

Optimization of Surfactant Concentration: For optimization of tristearin and tween 80 concentration, formulation was selected, keeping all other factors constant. The SLN formulations were prepared using different concentration of tristearin, tween 80 in aqueous medium **Table 3** and **Fig. 4**.

B. Optimization of Process Variables: Various process variables *i.e.* stirring speed stirring time and sonication time effect the formulation formulations were selected as the optimized formulation.

Optimization of Stirring Speed: Stirring speed of the stirrer was varied from 1000 to 4000 rpm for SLN preparation using the same formula of optimized formulation parameters and particle size and percentage drug entrapment were determined **Table 4** and **Fig. 5**.

Optimization of Stirring Time: For the optimization of stirring time was selected while other process variables were kept constant. The SLN dispersion was prepared with different stirring time 4hr given in following **Table 5**. Particle size and percentage drug entrapment were determined **Table 5** and **Fig. 6**.

Optimization of Sonication Time: Formulation was selected for the optimization time. SLN formulations were prepared with varying sonication time 4 min given in following **Table 6**. Particle size and percentage drug entrapment were determined (SBRL, Bhopal) **Table 6** and **Fig. 7**.

C. Optimized Parameter: The optimization studies were accomplished on the SLN formulation and the parameters used for the preparation of this optimized formulation.

Preparation of Solid Lipid Nanopartices by Solvent Evaporation Method: [5]

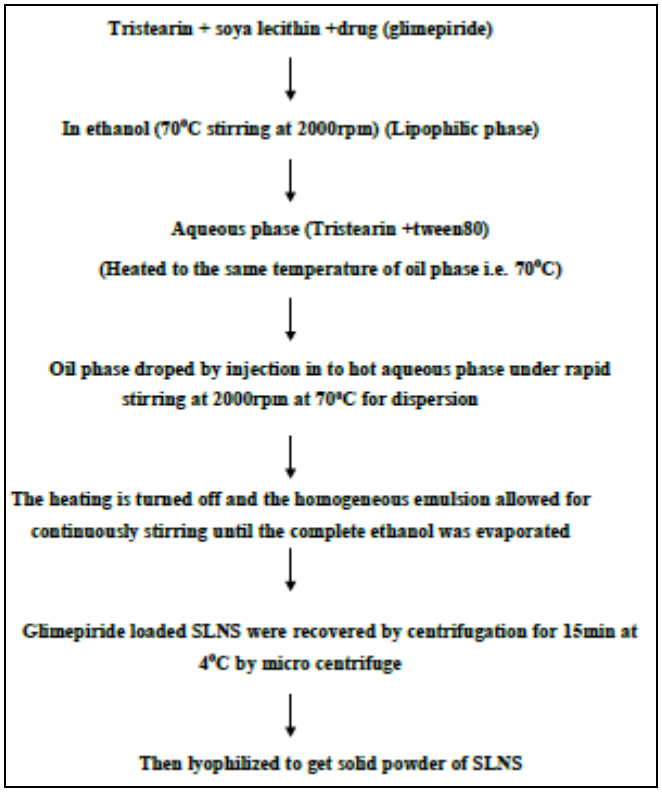

FIG. 1: PREPARATION OF SOLID LIPID NANOPARTICES

Characterization of the Solid Lipid Nanoparticle:

Particle Size and Polydispersity Index Determination: [6] For the determination of average particle size and polydispersity index of the solid lipid nanoparticle photon correlation spectroscopy using Zeta sizes (DTS Ver.4.10, Malvern Instruments England) was used. The sample of dispersion was diluted 1:9 v/v with de ionized water. The particle size distributions are represented by average size (diameter).

Surface Change Measurement: [6] The Zeta potential of the nanoparticles was determined by laser Doppler anemometry using a Malvern Zeta size also called Doppler Electro phoritic light scatter analyzer. The instrument is a laser-based multiple angle particle electrophoresis analyzer. Using Doppler frequency shifts in the measures the electrophoretic mobility (or Zeta potential) distribution together with the hydrodynamic size of particles (Size range -20 to -30 mv) in liquid suspension by photon correlation spectroscopy measurement.

Scanning Electron Microscopy (SEM): [7] Surface morphology was determined by Scanning EM (Nano Nova SEM-AMPRI) at Sapience bio analytical Reserch Lab. The sample for Scanning Electron Microscopy was prepared by lightly sprinkling the SLN powder on a double adhesive tape, which was stick on an aluminium stub. The Stubs were coated with gold to a thickness of about 300Aº using a sputter coated. All sample were examined under a scanning electron microscope at in acceleration voltage of 200 kv and photo-micrographs were taken at suitable magnification,

Transmission Electron Microscopy: [5] TEM was used as a visualizing aid for particle morphology. The sample (10 µl) was placed on the grids and allowed to stand at room temperature for 90 sec. Excess fluid was removed by touching the edge with filter paper. All sample were examined under a transmission electeration voltage of 100Kv and photo micrographs were taken at suitable magnification **Fig. 9**.

***In-vitro* Release of Glimepiride loaded SLN:** [8] Glimepiride release rates from the solid lipid nanoparticles were investigated through. Dialysis membrane having pore size of 2.4 nm and with molecular weight cut off 12,000-14,000 was used. The membrane was soaked in distilled water for 12h before mounting in a Franz diffusion Cell. Phosphate buffer saline (pH 7.4) was used as receptor fluid.

The SLN were diluted by addition of appropriate volume of phosphate buffer Saline. 1ml of diluted SLN was applied to upper donor chamber and temperature was maintained at 37 ± 5 ºC. An aliquot of 100 µl of sample was withdrawn from receiver compartment through side tube over 48 h. The fresh medium was replaced Glimepiride was calculated by determination of the amount of Glimepiride in receiver medium.

The concentration of Glimepiride in receiver medium was determined by UV-Vis spectro-photometer (UV-1800, 240v, Shimadzu Japan) **Table 7**.

Stability Study: The present study is desired to test the stability of Glimepiride loaded SLN Formulation. Stability test of SLNs was performed in term of particle size, zeta potential and % entrapment efficiency during storage. The optimized formulation was stored in screw capped amber coloured small glass bottle at 4 ± 1 ºC, 25 ± 2 ºC and 45 ± 2 ºC. Analysis of the sample was made Average particle size, zeta potential and % Entrapment efficiency after a period of 10, 20, 30 and 45 days under storage condition at 4 ºC, 25 ± 2ºC and at elevated temperature 45 ± 2 ºC **Table 8, 9, 10** and **11**.

Antidiabetic Study: Antidiabetic drugs are medicines developed to stabilise and control blood glucose levels amongst people with diabetes. Antidiabetic drugs are commonly used to manage diabetes. Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. There are a number of different types of antidiabetic drug including: Insulin Pramlintide (Amylin) GLP-1 receptor agonists (such as Byetta and Victoza). Oral hypoglycemics (tablets) Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in type I, which must be injected. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Type 2 diabetes mellitus is the most common type of diabetes. Treatments include (1) agents that increase the amount of insulin secreted by the pancreas, (2) agents that increase the sensitivity of target organs to insulin, and (3) agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

RESULTS AND DISCUSSION:

Optimization of Solid Lipid Nanoparticles Formulation:

A. Optimization of formulation variables

- **a)** Optimization of lipid/Lecithin ratio
- **b)** Optimization of Drug/Lipid ratio
- **c)** Optimization of Surfactant concentration

B. Optimization of Process variables

- **a)** Optimization of Stirring speed
- **b)** Optimization of Stirring time
- **c)** Optimization of Sonication time

A. Optimization of Formulation Variables:

a) Optimization of lipid / Lecithin ratio:

TABLE 1: OPTIMIZATION OF LIPID / LECITHIN RATIO

S. no.	Formulation code	Lipid/Lecithin ratio	Particle size nm	Polydispersity Index
1	F1	2:1	275 ± 4.01	0.668 ± 3.21
2	F2	1:1	262 ± 3.33	0.763 ± 3.6
3	F3	2:3	246 ± 3.06	0.788 ± 4.02
4	F4	1:2	225 ± 2.60	0.897 ± 3.61

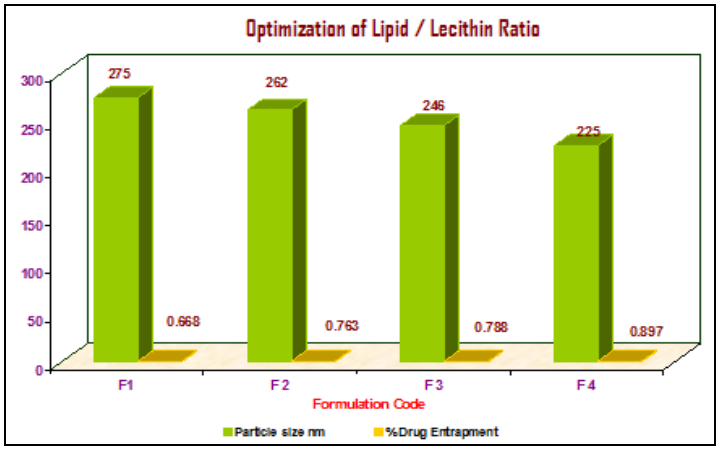

FIG. 2: OPTIMIZATION OF LIPID / LECITHIN RATIO

b) Optimization of Drug / Lipid Ratio:

TABLE 2: OPTIMIZATION OF DRUG / LIPID RATIO

S. no.	Formulation code	Drug/Lipids ratio	Particle Size nm	% Drug Entrapment
1	F1	1:10	287 ± 3.61	66.4 ± 0.82
2	F2	3:20	265 ± 2.33	70.8 ± 1.61
3	F3	1:5	270 ± 2.63	72.9 ± 3.43
4	F4	1:4	275 ± 3.21	75.5 ± 2.55

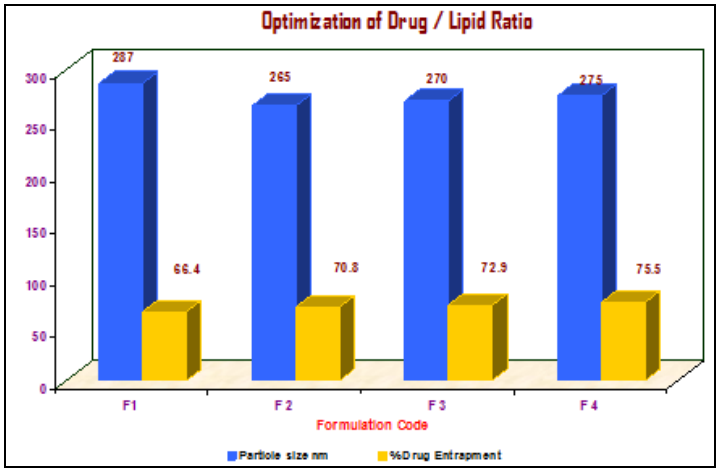

FIG. 3: OPTIMIZATION OF DRUG / LIPID RATIO

c) Optimization of Surfactant Concentration:

TABLE 3: OPTIMIZATION OF SURFACTANT CONCENTRATION

S. no.	Formulation code	Lipid/ Tween 80	Particle size nm	%Drug entrapment	Zeta Potential (MV)
1	F1	1:0.5%	265 ± 7.4	71 ± 2.2	-24 ± 3.3
2	F2	1:1%	245 ± 5.5	68 ± 1.1	-27 ± 7.7
3	F3	1:1.5%	240 ± 1.21	66 ± 0.6	-29 ± 4.1
4	F4	1:2%	236 ± 4.61	63 ± 8.5	-30 ± 1.4

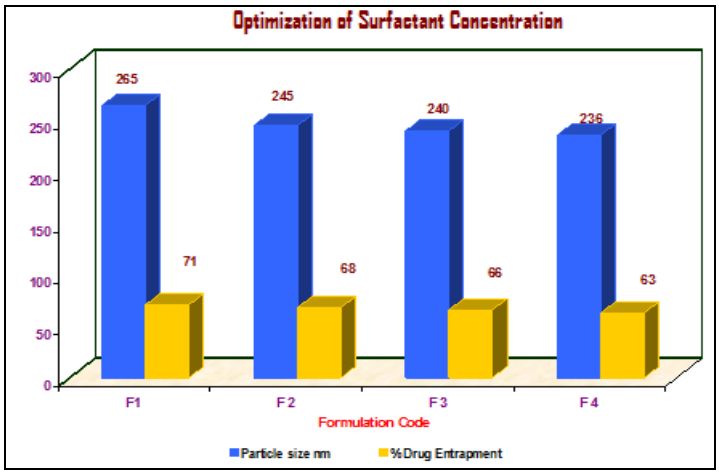

FIG. 4: OPTIMIZATION OF DRUG / LIPID RATIO

B. Optimization of Process Variables:

a) Optimization of Stirring Speed:

TABLE 4: OPTIMIZATION OF STIRRING SPEED

S. no.	Formulation code	Drug/Lipids ratio	Particle size nm	% Drug Entrapment
1	F1	~1000	236 ± 6.2	70.2 ± 1.63
2	F2	~2000	240 ± 3.14	68.5 ± 0.52
3	F3	~3000	255 ± 3.11	66.06 ± 0.80
4	F4	~4000	270 ± 4.12	63.30 ± 0.16

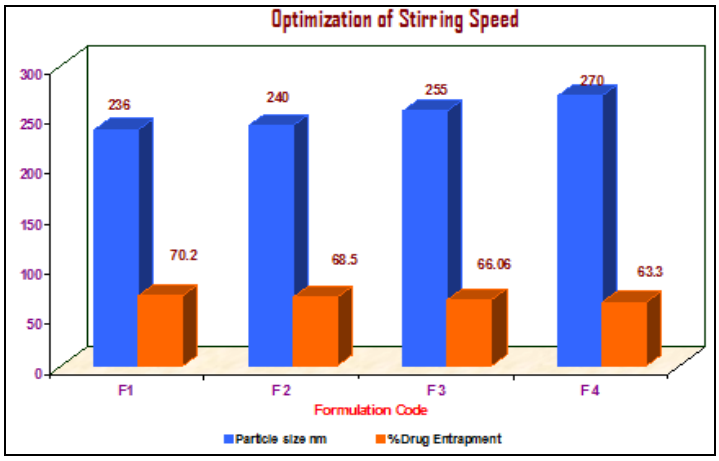

FIG. 5: OPTIMIZATION OF STIRRING SPEED

b) Optimization of Stirring Time:

TABLE 5: OPTIMIZATION OF STIRRING TIME

S. no.	Formulation code	Stirring time (h)	Particle size nm	% Drug Entrapment
1	F1	1 h	240.6 ± 2.02	66.33 ± 2.04
2	F2	2 h	245.3 ± 3.06	68.26 ± 0.88
3	F3	3 h	255.3 ± 3.02	66.6 ± 1.24
4	F4	4 h	265.2 ± 2.06	64.26 ± 2.33

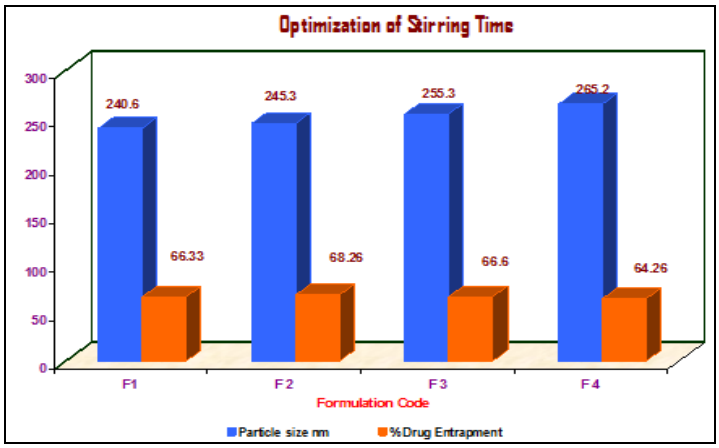

FIG. 6: OPTIMIZATION OF STIRRING TIME

c) Optimization of Sonication Time:

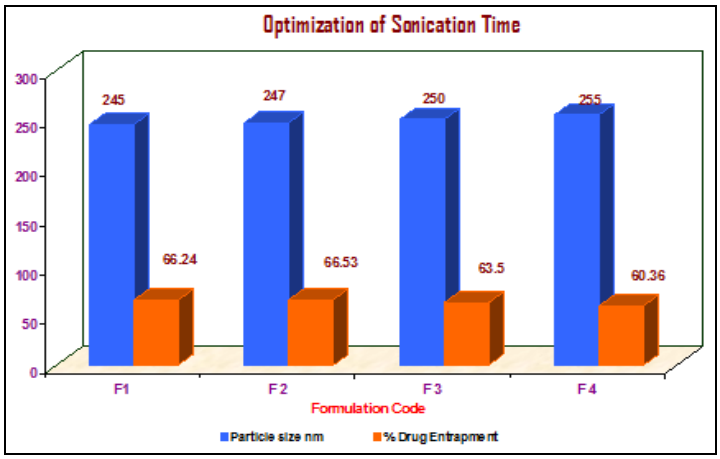

FIG. 7: OPTIMIZATION OF SONICATION TIME

TABLE 6: OPTIMIZATION OF SONICATION TIME

S. no.	Formulation code	Stirring time (min)	Particle size nm	% Drug Entrapment
1	F1	1 min	245 ± 3.15	66.24 ± 2.4
2	F2	2 min	247 ± 2.02	66.53 ± 0.23
3	F3	3 min	250 ± 3.41	63.50 ± 0.25
4	F4	4 min	255 ± 4.03	60.36 ± 2.64

TABLE 7: PARAMETERS AND OPTIMIZE VALUE

Parameters	Optimized value
Tristearin : Lecithin ratio	100:100 mg
Drug : Lecithin ratio	15:100 mg
Surfactant Concentration	1:0.5% wt/v
Stirring time	2 hr
Stirring speed	2000 rpm
Sonication time	2 min

Evaluation of Glimepiride Loaded Solid Lipid Nanoparticle:

Particle Size, Polidispersity Index and Zeta Potential: Particle size of the nanoparticles is presented as -z-average diameter which is basically mean hydrodynamic diameter of the particles. Particle size measurement was required to confirm the production of the particles in nano range. The result indicates that particle size was significantly influenced by most of the formulation and process variables.The tristearin amount was kept constant in all formulations with varying amount of soya lecithin among all these formulations with same amount of tristearin and soya lecithin was consider the ideal formulation. Then the formulation was selected with drug and lipid ratio with maximum % drug entrapment. Tween 80 was used as surfactant with varying concentration containing surfactant tristearin (1%) and tween80 (0.5%) was selected. Polydispersity index (P1) indicates with the size of the particle size distribution, which range from 0 to 1. Among all formulations f_2 produced SLNs with lowest PI and produced SLNs with high PI. Zeta potential (ZP) refers to the surface change of the particles. ZP (±) indicates the degree of repulsion between close and similarly charged particles in the dispersion. This repulsion force prevents aggregation of the particles.

Therefore, ZP is a useful parameter to predict the stability of the solid lipid nanoparticles dispersions. The Zeta potential was found to be given in **Table 8, 9, 10** and **11**.

Entrapment Efficiency: The EE% of the developed SLNs was shown a high amount of drug could be incorporated in nanoparticles dispersion. It can be seen that the encapsulated moiety in the SLNs in formulation is the highest entrapment efficiency of the optimized formulation.

The drug entrapment efficiency was measured using centrifugation method and all the Glimepiride –SLN formulations had average entrapment efficiency. The high EE might be beneficial to reduce the skin irritation of drug due to avoid.

Scanning Electron Microscopy (SEM): The SEM images of optimized formulation revealed that the particle size was in range with average particle size and also shows the surface morphology that the particles had nearly spherical shape shown in photomicrograph.

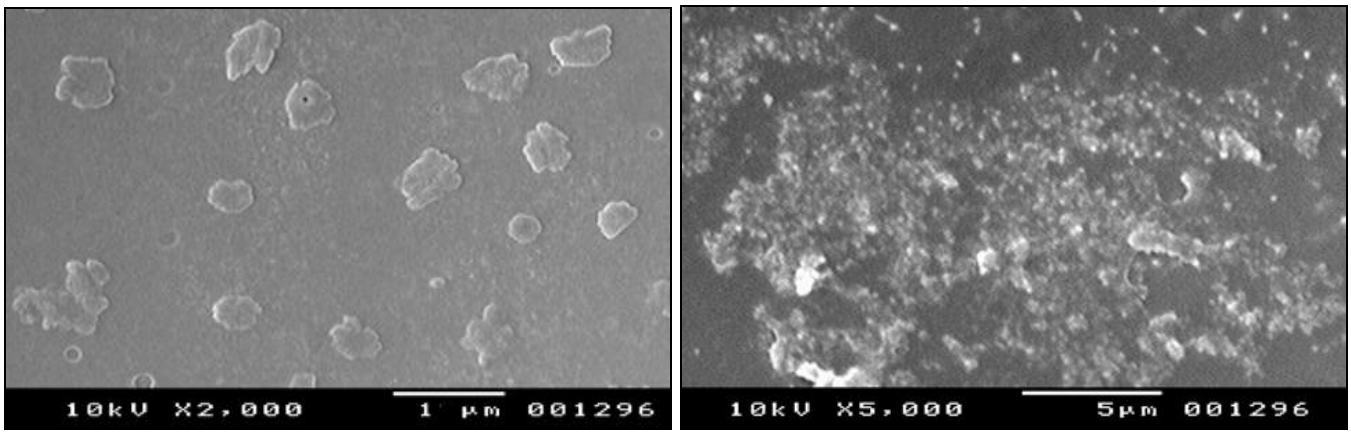

FIG. 8: SEM OF GLIMEPIRIDE LOADED SLN

The smallest particle size of SLN in SEM image observed. The SEM studies are performed with resolution of 2.00kv. A large no of particles have been observed in the SEM image in which same particles are smooth in surface while some with rough in surface. The smallest particle size observed in the image was well satisfying that the SLN are in range which was considered as the practical range of solid lipid nanoparticles. The drug release of Glimepiride loaded solid lipid nanoparticles imaging showed that Glimepiride. SLN revealed that the formulation of spherical nanoparticles with a smooth surface.

Transmission Electron Microscopy (TEM): The shape and surface morphology of optimized formulation Glimepiride lyophilized SLNs prepared *via* the solvent diffusion method were studied using TEM. In the TEM study, the size of the solid lipid nanoparticles was found range for all the samples. Drug/lipid ratio 15:100 particle size 265 ± 2.32 drug entrapment 70.8 ± 1.62. All the particles were found to be roughly spherical in shape with a well defined periphery. TEM image of optimized formulation. Glimepiride loaded SLNs also provides the structural in formation of the SLN. The solid lipid nanoparticles appear to be less dense in the core with a well-defined shell. No obvious aggregation of the solid lipid nanoparticles was observed in the TEM images.

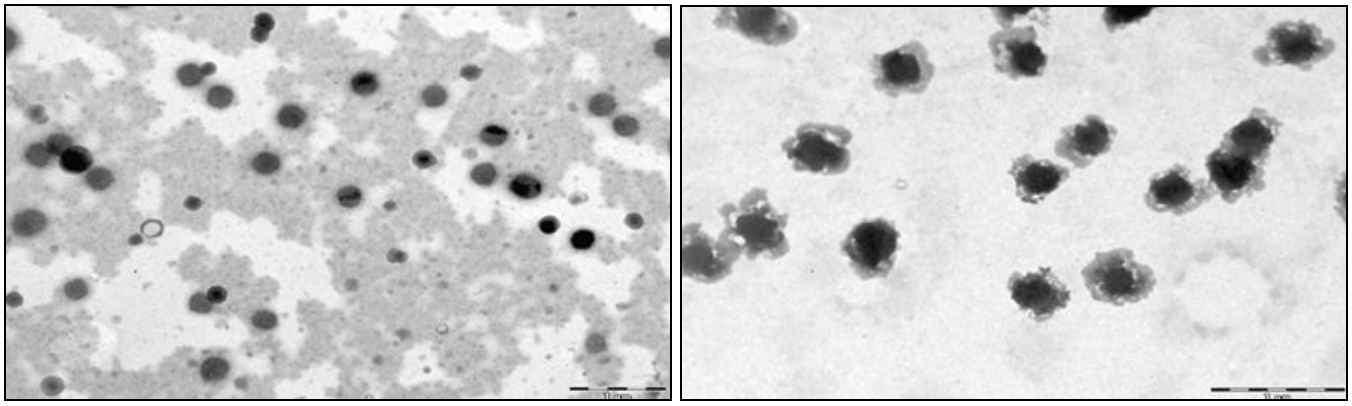

FIG. 9: TEM OF GLIMEPIRIDE LOADED SLN

The TEM imaging of optimized formulation. Glimepiride SLN was shown in photomicrograph 7.15. Drug/lipids ratio15:100. The particle size 265 ± 2.32 of Glimepiride SLN from TEM images accords with that from that form photon correlation Spectroscopy use of different concentrations of surfactant exhibited a spherical shape and had a narrow size distribution Drug entrapment 70.8 ± 1.62. The TEM image of the Montenegro L *et al*., 2012.

In-vitro Release of Glimepiride Loaded Solid Lipid Nanoparticles:

TABLE 8: *IN-VITRO* RELEASE OF GLIMEPIRIDE LOADED SOLID LIPID NANOPARTICLES

Time (h)	Cumulative % Drug Release
0	0
1	4.56
2	9.96
4	15.53
6	22.23
8	33.04
10	42.09
12	51.17
24	57.23
48	63.74

TABLE 9: EFFECT OF STORAGE ON THE PARTICLE SIZE, ZETA POTENTIAL AND PERCENTAGE ENTRAPMENT EFFICIENCY AT 4 ± 1 ºC

S. no.	Parameters	Time (in days)				
		0	10	20	30	45
1	Particle size	109 ± 2.1	109 ± 2.01	109 ± 2.01	119 ± 3.31	132 ± 0.6
2	Zeta potential	-27.5 ± 1.8	-27 ± 1.8	-26.5 ± 1.8	-26 ± 4.6	-25 ± 3.23
3	Entrapment efficiency	63.5 ± 4.5	63.53 ± 4.5	63.53 ± 4.5	62.23 ± 2.3	62.73 ± 5.2

TABLE 10: EFFECT OF STORAGE ON THE PARTICLE SIZE, ZETA POTENTIAL AND PERCENTAGE ENTRAPMENT EFFICIENCY AT 25 ± 2 ºC

S. no.	Parameters	Time (in days)				
		0	10	20	30	45
1	Particle size	109 ± 2.0	113 ± 5.32	115 ± 3.2	120 ± 2.3	125 ± 0.96
2	Zeta potential	-27.5 ± 1.8	-27.5 ± 1.8	-27 ± 1.8	-25 ± 4.6	-23 ± 3.23
3	Entrapment efficiency	63.53 ± 4.5	62.53 ± 4.5	62.23 ± 4	61.53 ± 1.3	60.53 ± 3.2

Result has been expressed as mean± SD (n=3)

TABLE 11: EFFECT OF STORAGE ON THE PARTICLE SIZE, ZETA POTENTIAL AND PERCENTAGE ENTRAPMENT EFFICIENCY AT 45 ± 2 ºC

S. no.	Parameters	Time (in days)				
		0	10	20	30	45
1	Particle size	109 ± 2.01	115 ± 3.52	132 ± 1.24	154 ± 2.35	166 ± 0.56
2	Zeta potential	-27.5 ± 1.8	-28 ± 1.2	-30 ± 3.1	-30 ± 3.6	-32 ± 2.33
3	Entrapment efficiency	63.53 ± 4.5	60.43 ± 2.2	57.32 ± 1.2	54.21 ± 5.1	51.73 ± 1.2

The slow and sustained hypoglycemic response could be due to slow release of drug from SLN. In orally treated group, the hypoglycemic effect was reduced up to 10 h, which could be due to its short biological half life. The oral route produced severe hypoglycemia in initial hours, where as there was no such effect in the case of transdermal patches. The pharmacokinetic parameters obtained with transdermal SLN patches were significantly ($p<0.05$) different from orally treated group. This could be a fast absorption and short half life. Whereas SLN through transdermal route showed slow release of drug from lipid vesicles and maintained peak plasma concentration over a prolonged period. Transdermal SLN system would also protect the formulation from dehydration and accidental damage, leakage of drug from SLN. Glimepiride is an anti-diabetic, oral hypoglycemic agent of meglitinide class used in the management of type II diabetes mellitus. In the present scenario there are different dosage forms available in the market for diabetes mellitus. These dosage forms are either taken orally or parentally. Both type of dosage forms have their disadvantages, like in case of parenteral dosage form, main disadvantage is patient compliance and in case of oral dosage forms, they are taken after meal every time (2 to 3 time in a day).

CONCLUSION: Therefore, an attempt has been made to develop a nanoparticulate dosage form of Glimepiride with different lipid carriers and mixtures of surfactants. The nanoparticles were formulated by High pressure homogenization. Prepared drug loaded SLNs were evaluated for particle size analysis, FTIR spectroscopy, DSC, Drug entrapment efficiency, SEM and *in-vitro* release studies.

An optimum lipid ratio (100:100) was selected as it showed optimum size of 262 ± 3.33 nm and a PDI of 0.763 ± 3.6. As the concentration of lecithin was increased particle size also increased also with an increased in PDI was observed hence an optimized ratio was selected.

The present research work could be concluded as successful development of solid lipid particles of an antidiabetic drug Glimepiride using solid lipid (tristearin) and co-lipid (soya lecithin) by solvent-evaporation method. The Glimepiride loaded SLNs presented a suitable particle size, zeta potential polydispersity index, entrapment efficiency and *in-vitro* drug release. The SEM and TEM images also revealed the formation of SLNs in nano-sized spherical particles with smooth surface. The SLNs were more stable at 4 °C than 45 °C, the particle size increased more with decrease in entrapment efficiency at 45 °C than 4 °C.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

Future Scope:

- ✓ The research work can be further continued for release profile using blends of different lipid carriers for making SLNs more stable.
- ✓ The process optimization can be carried out by studying different variables such as different surfactants and time of homogenization.

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