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FORMULATION AND EVALUATION OF GLIMEPIRIDE LOADED TRANSETHOSOME FOR TREATMENT OF DIABETES

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ABSTRACT

The present study focuses on the formulation, optimization, and evaluation of Glimepiride-loaded transethosomal gel for enhanced transdermal drug delivery in the treatment of type 2 diabetes mellitus. Glimepiride, a poorly water-soluble sulfonylurea, suffers from variable oral bioavailability and hepatic first-pass metabolism, which limits its therapeutic efficacy. To overcome these challenges, transethosomes a novel class of ultra-deformable lipid vesicles were employed to improve the drug's skin permeation and sustained release characteristics. A series of fourteen formulations (F1–F14) were prepared by varying lipid ratios, ethanol concentration, drug content, and stirring duration. Among them, formulation F12 was optimized based on its smallest vesicle size (125.36 nm), high entrapment efficiency (74.65%), and stable zeta potential (-40.36 mV). The optimized formulation was incorporated into a gel base and evaluated for viscosity, drug content, spreadability, extrudability, and *in vitro* drug release. The gel exhibited suitable viscosity (3510 ± 20 cps), uniform drug distribution ($99.45 \pm 0.15\%$), and favorable spreadability and extrudability. *In vitro* release studies revealed a sustained drug release profile, with 94.65% cumulative drug release over 10 hours. Kinetic modeling indicated that the drug release followed the Higuchi model ($R^2 = 0.9837$), confirming diffusion-controlled release. The Glimepiride-loaded transethosomal gel demonstrated excellent physicochemical properties, enhanced drug release behavior, and potential for improved therapeutic efficacy through transdermal application. This delivery system may offer a promising alternative to conventional oral administration of Glimepiride, improving patient compliance and minimizing systemic side effects.

Keywords: Glimepiride; Transethosomes; Transdermal drug delivery; Vesicle size; Entrapment efficiency; Zeta potential; Sustained release; Higuchi model; Diabetes mellitus; Topical gel.

INTRODUCTION

Diabetes mellitus is a complex and progressive metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is categorized primarily into type 1 and type 2 diabetes, with type 2 diabetes mellitus (T2DM) being the most prevalent form, accounting for over 90% of diabetes cases globally. Prolonged hyperglycemia in diabetic patients is associated with severe complications including neuropathy, nephropathy, retinopathy, and cardiovascular disorders, thereby contributing significantly to morbidity and mortality worldwide (American

Diabetes Association, 2014; International Diabetes Federation, 2021).

Glimepiride is a third-generation sulfonylurea widely used for the management of T2DM. It lowers blood glucose levels by stimulating insulin secretion from pancreatic β-cells and increasing insulin sensitivity in peripheral tissues. However, Glimepiride is a Biopharmaceutical Classification System (BCS) Class II drug, characterized by low aqueous solubility and high permeability, which leads to poor and variable oral bioavailability. In addition, oral administration is associated with first-pass hepatic metabolism, gastrointestinal side effects, and the risk of hypoglycemia, especially with higher doses (Rosenstock *et al.,* 2001; Gandhi *et al.*, 2011).

To address these limitations, transdermal drug delivery systems (TDDS) have gained increasing attention as an alternative route. Among these, transethosomes represent a novel class of ultra-deformable lipid vesicles composed of phospholipids, ethanol, and edge activators such as surfactants. These vesicles enhance drug permeation through the stratum corneum due to their flexibility and ethanol-induced disruption of skin lipid bilayers (Cevc *et al.,* 1992; Jain *et al.,* 2003). Transethosomes are capable of encapsulating both hydrophilic and lipophilic drugs and offer improved stability, prolonged drug release, and enhanced skin penetration compared to conventional liposomes and ethosomes (Elsayed *et al.,* 2007; Honeywell-Nguyen *et al.,* 2005).

Moreover, incorporating transethosomes into a gel base improves the formulation's viscosity, spreadability, and patient compliance. The gel system serves as a suitable carrier for topical application and facilitates uniform distribution of the vesicular formulation over the skin, while also enhancing its residence time.

The objective of the present study is to develop and evaluate a Glimepiride-loaded transethosomal gel for the effective transdermal management of type 2 diabetes. The formulation was optimized by systematically varying lipid ratios, ethanol content, drug concentration, and stirring time. The optimized formulation was characterized for vesicle size, zeta potential, entrapment efficiency, *in vitro* drug release, and stability. This novel delivery system is expected to overcome the drawbacks of oral Glimepiride and provide a more effective and patient-friendly alternative for diabetes management.

MATERIALS AND METHODS

Materials

The materials used for the formulation development of Glimepiride-loaded blend microspheres included pharmaceutical-grade chemicals obtained from reputed suppliers. Glimepiride was received as a gift sample from Bioplus Life Sciences Pvt. Ltd., Bangalore. Soya phosphatidylcholine (Soya PC) was procured from HiMedia Laboratories Pvt. Ltd., Thane, while Span 20 and Carbopol were sourced from Loba Chemie Pvt. Ltd., Mumbai. Solvents such as ethanol, methanol, chloroform, and reagents including propylene glycol, hydrochloric acid, sodium hydroxide, and potassium dihydrogen phosphate were obtained from Qualigens Fine Chemicals, Mumbai. Buffer components like disodium hydrogen phosphate and dipotassium hydrogen orthophosphate were supplied by S. D. Fine Chem. Ltd., Mumbai. All chemicals

used were of analytical or laboratory grade and were used without further purification.

Methods

Formulation and Development of Glimepiride-Loaded Transethosomes

The required quantities of soya phosphatidylcholine (Soya PC) and surfactant were accurately weighed and dissolved in ethanol in a round-bottom flask with gentle shaking, as described by Shaji (2014). A thin lipid film was formed using a rotary evaporator operated at 25℃, 600 mmHg pressure, and 100 rpm for 15 minutes. The residual solvent was further removed by passing a stream of nitrogen gas over the film. To ensure complete solvent removal, the lipid film was placed in a desiccator for at least 12 hours.

Separately, Glimepiride was dissolved in 10 mL of phosphate buffer (pH 7.4), preheated to 55℃. This buffer solution was then used to hydrate the lipid film by gentle hand shaking for 30 minutes. The hydrated mixture was further subjected to shaking on an orbital shaker for 30 minutes to ensure uniform dispersion. The resulting transethosomal suspension was visually examined under a microscope and stored at 4℃ for further use.

Preparation of Gel Base

Carbopol 934 (1% w/v) was accurately weighed and slowly dispersed in 80 mL of double distilled water in a beaker. The dispersion was stirred continuously at 800 rpm for 1 hour. Following this, 10 mL of propylene glycol was added gradually to the mixture. The volume was adjusted to 100 mL with distilled water, and the mixture was sonicated in a bath sonicator for 10 minutes to eliminate air bubbles. The pH of the gel was adjusted to 6.8. The optimized transethosomal formulation containing Glimepiride (equivalent to 0.1% w/w) was then incorporated into the gel base to obtain the desired drug-loaded transethosomal gel (Garg *et al.*, 2014).

Characterization of Glimepiride loaded Transethosomes

Surface charge and vesicle size

The vesicles size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK) (Kumar *et al.*, 2016). The Zeta potential of the Transethosomes was calculated from their electrophoretic mobility according to Helmholtz–Smoluchowsky. A Zetasizer was employed on a large bore measuring cell to measure Zeta potential with a field strength of 20 V/cm. Samples were diluted with 0.9 % NaCl adjusted to a conductivity of 50 lS/cm.

Entrapment efficiency

One milliliter of Transethosomes suspension was centrifuged at 15.000 rpm for 1 h to allow to separate the entrapped drug from the un-entrapped drug (Song *et al.*, 2012). After removal of the supernatant, the sediment was lysed using methanol and then analyzed spectrophotometrically at 228nm using a UV spectrophotometer (Labindia 3000+). The Entrapment efficiency % of drug in the prepared Transethosomes was calculated applying the following equation:

$$\% \ Entrapment \ Efficiency = \frac{Therotical \ drug \ content - Practical \ drug \ content}{\text{Therotical drug content}} \times 100$$

Characterization of Transethosomes containing gel

Measurement of Viscosity

Viscosity measurements of prepared topical Transethosomes based gel were measured by

Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; viscosity (Ahad *et al.,* 2014).

pH measurements

pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. Following calibration, the electrode was dipped into the vesicles for as long as the vesicles covered it. The pH of a chosen formulation was then measured, and the results were recorded on the display.

Drug Content

In a beaker, 100 mg of topical Transethosomes gel was accurately weighed, and 20 ml of methanol was added (Jardan *et al.,* 2023). This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol. This solution was analyzed using UV-Spectroscope at λ_{max} 228nm.

Extrudability study

Extrudability was determined by the amount of gel extruded from a collapsible tube when a specific weight was applied (Chourasia *et al.,* 2011). Extrudability improves as the amount of gel extruded increases. It was calculated by weighing a gel-filled collapsible tube and recording the weight at which the gel was extruded from the tube.

Spreadibility

Spreadability of the formulation is required to ensure that an adequate dosage is accessible for absorption via the skin, resulting in a positive therapeutic response. A slide is placed on a wooden block, and the top slide is moveable, with one end of the movable slide attached to a weight pan (Rakesh and Anoop, 2012). To assess spreadibility, 2-5 g of gel was placed between two slides, and the weight was gradually raised by adding it to the weight pan, with the time taken by the top plate to cover a distance of 6cm after adding 20g of weight being recorded. Spreadability indicates a shorter time to spread.

$$Spreadibility\,(g.cm/\sec) = \frac{Weight\ tide\ to\ Upper\ Slide \times Lenth\ moved\ on\ the\ glass\ slide}{Time\ taken\ to\ slide}$$

***In vitro* drug diffusion study**

The *In-vitro* diffusion study is carried by using Franz Diffusion Cell. Egg membrane is taken as semi permeable membrane for diffusion (Korsmeyer *et al.,* 1983). The Franz diffusion cell has receptor compartment with an effective volume approximately 30mL and effective surface area of permeation 3.14sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. A Teflon-coated magnetic bead is inserted in the diffusion cell and stirs the receptor fluid. At the end of each sampling period, samples are removed and replaced with equal quantities of fresh receptor fluid. The removed samples are spectrophotometrically examined at the drug's wavelength of 228nm.

RESULTS AND DISCUSSION

The development and evaluation of Glimepiride-loaded transethosomes aimed to enhance the drug's solubility, skin

permeation, and sustained release for effective transdermal delivery in the management of type 2 diabetes mellitus. A total of 14 formulations (F1–F14) were prepared and evaluated for average vesicle size and entrapment efficiency (Table 5).

Among the various formulations, F12 exhibited the smallest vesicle size (125.36 nm) and high entrapment efficiency (74.65%), indicating optimal composition and processing parameters. This result suggests that the formulation had efficient encapsulation of the drug within the vesicles and possessed the necessary nano-size required for effective skin permeation. The vesicle size significantly decreased with optimized stirring duration and ethanol content, while still maintaining entrapment efficiency above 70%.

Table 6 and Figures 1 & 2 detail the characterization of the optimized formulation F12, which also demonstrated a zeta potential of -40.36 mV. The negative surface charge indicates electrostatic stability, suggesting that the vesicles are unlikely to aggregate, thereby ensuring physical stability of the dispersion over time. Vesicle size within the nanoscale range and sufficient surface charge are essential for enhancing the vesicular penetration through the stratum corneum.

The optimized transethosomal formulation was then incorporated into a gel base and evaluated for physicochemical properties, with the results shown in Table 7. The gel exhibited good viscosity (3510 ± 20 cps), appropriate for topical application, and a high drug assay value ($99.45 \pm 0.15\%$), confirming uniform drug distribution. The extrudability (180 ± 12 g) and spreadability (12.36 ± 0.45 g·cm/sec) were within acceptable limits, suggesting that the gel would be easy to apply and would evenly spread over the skin surface.

The *in vitro* drug release study of the transethosomal gel (Table 8) showed a sustained release profile, with 94.65% cumulative drug release over 10 hours. The initial burst release (14.65% at 0.5 hours) was followed by a controlled release phase, which is advantageous in maintaining therapeutic plasma concentrations over extended periods. This pattern reflects the successful encapsulation of Glimepiride within the transethosomal vesicles and the ability of the gel base to prolong drug release.

To better understand the release mechanism, regression analysis was performed using various kinetic models. As seen in Table 9, the release data best fit the Higuchi model ($R^2 = 0.9837$), indicating that drug release was predominantly governed by a diffusion-controlled mechanism. The Korsmeyer–Peppas model ($R^2 = 0.9724$) further supported this observation, suggesting Fickian diffusion as the principal mode of drug transport from the gel matrix.

Table 1: Optimization of ratio of lipid concentration

Formulation code	Soya PC: Span 20 (% w/v)	Ethanol	Drug (% w/v)	Average vesicle size (nm)	% entrapment efficiency
F1	9.5:0.5	10	1.0	310.25	68.85
F2	9:1	10	1.0	295.65	73.32
F3	8:2	10	1.0	255.45	79.98
F4	7:3	10	1.0	268.96	74.65

Table 2: Optimization of ethanol concentration

Formulation code	Soya PC: Span 20 (% w/v)	Ethanol	Drug (% w/v)	Average vesicle size (nm)	% entrapment efficiency
F5	8:2	5	1.0	285.45	70.32
F6	8:2	10	1.0	215.65	76.65
F7	8:2	15	1.0	266.65	70.36
F8	8:2	20	1.0	274.63	69.98

Table 3: Optimization of drug concentration

Formulation code	Soya PC: Span 20 (% w/v)	Drug (% w/v)	Ethanol (ml)	Average vesicle size (nm)	% Entrapment efficiency
F9	8:2	1.0	10	185.65	75.32
F10	8:2	1.5	10	210.36	70.36
F11	8:2	2.0	10	205.65	69.98

Table 4: Optimization of Stirrer duration

Formulation code	Soya PC: Span 20 (% w/v)	Drug (% w/v)	Stirrer duration (min)	Average vesicle size (nm)	% Entrapment efficiency
F12	8:2	1.0	5	125.36	74.65
F13	8:2	1.0	10	130.52	68.85
F14	8:2	1.0	15	115.63	66.65

Table 5: Results of Average vesicle size and % Entrapment efficiency of prepared Transethosomes formulation

Formulation code	Average vesicle size (nm)	% Entrapment efficiency
F1	310.25	68.85
F2	295.65	73.32
F3	255.45	79.98
F4	268.96	74.65
F5	285.45	70.32
F6	215.65	76.65
F7	266.65	70.36
F8	274.63	69.98
F9	185.65	75.32
F10	210.36	70.36
F11	205.65	69.98
F12	125.36	74.65
F13	130.52	68.85
F14	115.63	66.65

Table 6: Characterization of Optimized formulation of transethosomes

Characterization	Average vesicle size (nm)	% Entrapment efficiency	Zeta Potential (mV)
F12	125.36	74.65	- 40.36

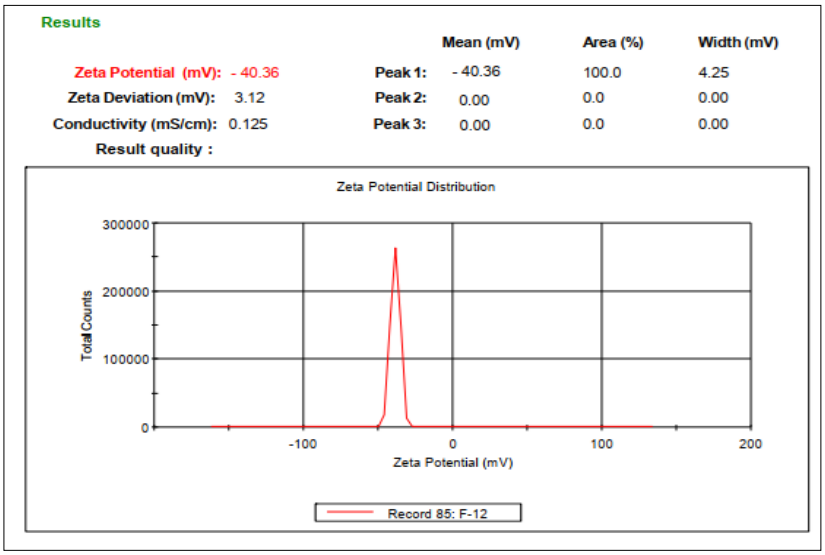

Figure 1: Image of Average vesicle size of optimized formulation F12

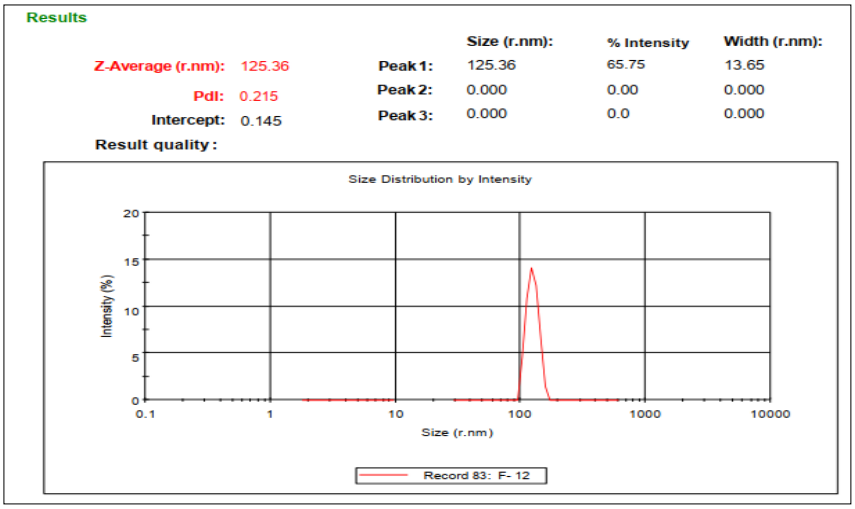

Figure 2: Image of Zeta Potential of optimized formulation F12

Table 7: Characterization of gel formulation containing Glimepiride loaded Transethosomes

Formulation	Viscosity* (cps)	Assay* (%)	Extrudability* (g)	Spreadability* (g.cm/sec)
Gel formulation	3510±20	9945±0.15	180±12	12.36±0.45

Table 8: *In vitro* drug release study of prepared gel formulation

S. No.	Time (hr)	% Cumulative Drug Release*
1	0.5	14.65
2	1	20.36
3	1.5	33.32
4	2	45.85
5	4	55.69
6	6	69.98
7	8	88.78
8	10	94.65

*Average of three determination

Table 9: Regression analysis data of transethosomes gel formulation

Batch	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas Equation
	R^2			
Optimized gel formulation	0.9511	0.9593	0.9837	0.9724

CONCLUSION

The optimized Glimepiride-loaded transethosomal gel formulation demonstrated excellent vesicle characteristics, stability, drug entrapment, mechanical properties, and a controlled release profile. These attributes make it a promising candidate for transdermal delivery of Glimepiride, offering potential advantages over conventional oral therapy such as improved bioavailability, reduced side effects, and enhanced patient compliance.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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