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## FORMULATION AND EVALUATION OF GLICLAZIDE ETHOSOMES AS A NOVEL DRUG CARRIER

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### Keywords:

Gliclazide, ethosomes, transdermal, vesicular carrier, anti-diabetic, phospholipid, lecithin

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**ABSTRACT:** The main aim of the present investigation was to evaluate transdermal potential ethosomes bearing anti-diabetic drug Gliclazide. Total eight formulations (F<sub>1</sub>-F<sub>8</sub>) of ethosomes were prepared by using cold method with three different concentrations of phospholipid (0.5, 1, 2 % w/w) and ethanol (10, 20, 30 % v/v) and it was compared with hydroethanolic solution. They were evaluated for vesicular shape, size, entrapment efficiency and *in-vitro* studies. The formulation F<sub>6</sub> (ethanol 20 % v/v and phospholipid (1 % w/w) was selected as the best formulation due to its optimum vesicle size, entrapment efficiency, less turbidity and maximum *in-vitro* release. The stability studies performed on F<sub>6</sub> formulation at two different temperatures of 25° ± 2°C and 4° ± 2°C for the period of 6 months also shows the satisfactory results. It was further incorporated into gel using carbopol 934 (1, 1.5, 2 % w/w) as a base. The carbopol concentration of 1.5% w/w gives the maximum *in-vitro* release of 96.06 ± 0.16 % in dialysis membrane and *ex-vivo* release of 79.67 ± 0.35 % in case of skin of mice. The results showed the potential of ethosomes of being a safe and very efficient drug carrier for transdermal delivery of drug.

**INTRODUCTION:** Diabetes mellitus is the most common endocrine disorder affecting around 2-3% of the population worldwide and its incidence is rising day by day. In the year 2000, 150 million people worldwide had diabetes and expected to double by this year. By 2030, the WHO estimates that the number of people with diabetes will almost double to 366 million. More than 220 million people worldwide have diabetes and almost 80% of the people die with diabetes in low and middle-income countries<sup>1-2</sup>. Diabetes mellitus is a heterogeneous group of metabolic disorder characterized by chronic hyperglycemia with disturbance of carbohydrate, protein and fat metabolism. There are two major types of diabetes mellitus -Type 1: Insulin dependent diabetes mellitus (IDDM) and Type 2: Non-insulin dependent diabetes mellitus (NIDDM)<sup>3-7</sup>.

Second generation sulfonylurea are 20-100 times more potent than first generation sulfonylurea. Glibenclamide, Glimepride, Glipizide, Gliclazide are the second generation sulfonylurea class of insulin secretagogues used in management of non-insulin dependent diabetes mellitus (NIDDM). The sulfonylurea acts by stimulating β-cells of pancreas to release insulin. It increases both basal insulin secretion and meal stimulated insulin release. It also increases peripheral glucose utilization; decrease gluconeogenesis; increases number and sensitivity of insulin receptor. Gliclazide has demonstrated superior efficacy and safety and lower incidence of hypoglycemia compared to other sulfonylureas<sup>8-11</sup>.

Ethosomes are soft, malleable ethanol containing novel vesicular carriers that transport active substances through stratum corneum into the deeper layers of the skin. The high concentrations of ethanol cause inter – digitation effect on the lipid barriers, allows vesicles to penetrate through stratum corneum barrier. These novel vesicles showed enhanced permeation, increased bioavailability with no toxic raw materials

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compared to liposomes<sup>12-14</sup>. The main objective of the present study was to formulate and evaluate ethosomal suspensions and ethosomal gels containing Gliclazide and their comparative study.

## MATERIALS AND METHODS:

### Materials:

Gliclazide, Phospholipid, ethanol and propylene glycol were purchased from S.d fine chem. Limited, Mumbai, India. All other reagents and solvents were of analytical grade.

### Methods:

#### Fourier Transform-Infrared Ray Spectroscopy Studies (FT-IR) Studies:

The interaction studies between drug, phospholipid and carbopol were studied using *FT-IR* spectroscopy. Spectra of Gliclazide, phospholipid carbopol and physical mixture of Gliclazide phospholipid and carbopol were compared at 400 – 4000  $\text{cm}^{-1}$ .

### Formulation of Gliclazide ethosomal suspension:

Ethosomal formulation of Gliclazide was prepared by cold method<sup>15-17</sup>. The ethosomal formulation prepared here comprised of 0.5 – 2% w/w phospholipids, 10 – 30% v/v ethanol, drug (80 mg), 10% v/v propylene glycol and water added to 100% v/v. Phospholipid and drug were dissolved in ethanol propylene glycol mixture. The mixture was heated to 30°C in water bath. The double distilled water heated to 30°C was added drop wise with continuous stirring at 1700 rpm in a closed vessel.

The system was kept at 30°C throughout the preparation. Mixing was continued for additional half an hour. The ethosomal suspension prepared here was finally sonicated using probe sonicator at 4°C in 3 cycles of 5 minutes and 5 minutes rest between the cycles. The nanosized ethosomes were formed spontaneously in this method. The vesicular preparation was stored at 4°C overnight. The composition of ethosomal vesicles is mentioned in

**Table 1**

**TABLE: 1 COMPOSITION OF GLICLAZIDE ETHOSOMES:**

FORMULATION CODE	DRUG (% w/w)	LECITHIN (% w/w)	ETHANOL (% v/v)	PROPYLENE GLYCOL (% v/v)
F <sub>1</sub>	0.08	0.5	10	10
F <sub>2</sub>	0.08	0.5	20	10
F <sub>3</sub>	0.08	0.5	30	10
F <sub>4</sub>	0.08	1	10	10
F <sub>5</sub>	0.08	1	20	10
F <sub>6</sub>	0.08	1	30	10
F <sub>7</sub>	0.08	2	20	10
F <sub>8</sub>	0.08	2	30	10
F <sub>9</sub>	0.08	-	20	10

### Preparation of hydroethanolic formulation:

The hydroethanolic formulation was prepared by dissolving drug in ethanol propylene glycol mixture. The mixture was heated to 30°C in a water bath. The double distilled water heated to 30°C was added drop wise with continuous stirring at 1700 rpm in a closed vessel. The system was kept 30°C throughout the preparation. Mixing was continued for an additional half an hour. This solution prepared was finally sonicated using probe sonicator as earlier. Finally the preparation was stored at 4°C overnight.

### Formulation of Gliclazide ethosomal gel:

The ethosomal vesicle showing the highest release profile (F<sub>6</sub>) was further incorporated in to carbopol gel. The specified amount of carbopol (1%, 1.5%

and 2% w/w) was added in minimum amount of distilled water and soaked overnight. The ethosomal preparation was added to the swollen polymer with continuous stirring at 700 rpm in a closed vessel. The mixing was continued until homogenous ethosomal gels were obtained. The temperature was maintained 30°C throughout the preparation. The pH was then adjusted to neutral by using triethanolamine.

### Formulation of Gliclazide gel:

Gliclazide gel containing carbopol (1.5 %w/w) was soaked overnight in distilled water. Then suitable amount of buffer was added to the solution with constant stirring by magnetic stirrer at 700 rpm. The temperature of 30°C was maintained throughout the preparation. Then drug dissolved in

suitable amount of buffer was added to the solution. The mixing was continued until homogenous gel was obtained and pH was adjusted to neutral by using triethanolamine.

**TABLE 2: FORMULATIONS OF GLICLAZIDE ETHOSOMAL AND PLAIN DRUG (PD) GEL**

Gel Formulation Code	Carbopol (%W/W)	Triethanolamine (% W/W)	Phosphate Buffer
G <sub>1</sub>	1	0.5	q.s.
G <sub>2</sub>	1.5	0.5	q.s.
G <sub>3</sub>	2	0.5	q.s.
PD	1.5	0.5	q.s.

### Evaluation of Gliclazide Ethosomes:

#### i) Optical microscopy:

A drop of ethosomal suspension before sonication was spread on a slide and covered with cover slip. Then it was observed by optical microscope and photomicrographs were taken.

#### ii) Scanning electron microscopy (SEM):

One drop of ethosomal system was mounted on a stub covered with clean glass homogeneously. A polaron E5 100 sputter coat the samples with gold and the samples were examined under a scanning electron microscope at an accelerating voltage of 20 KV.

#### iii) Entrapment efficiency:

The entrapment efficiency of ethosomes of Gliclazide was determined by ultra centrifugation technique. 15 ml of ethosomal formulation was taken in a centrifuge tube and allowed to centrifuge at 12000 rpm for 2 hour. Then total volume of supernatant was measured. Then amount of drug in the supernatant layer was determined by using UV spectrophotometer at 225.4 nm. The entrapment efficiency was calculated by using following formula:

$$\text{Entrapment Efficiency} = \left[ \frac{Q_t - Q_s}{Q_t} \right] \times 100$$

Where, Q<sub>t</sub> is the amount of drug added

Q<sub>s</sub> is the amount of drug detected in the supernatant.

#### iv) Turbidity measurement:

Digital Nephalo-Turbidity Meter 132 was used to measure the turbidity of all the ethosomal suspensions. In this method 500 NTU

(Nephelometric Turbidity Units) range is set and zero reading was set with milipore water. The ethosomal formulations were transferred to glass cuvette of capacity 50 ml. the holder was then placed inside the instrument. The turbidity measurement was displayed on the screen and expressed as NTU.

#### v) *In-vitro* release through dialysis membrane:

The *in-vitro* permeation studies were done using Franz Diffusion cell. The dialysis membrane was soaked overnight in phosphate buffer 7.4. The dialysis membrane was clamped between donor compartment and receiver compartment. 5 ml of the ethosomal formulation was kept evenly in the donor compartment.

The receiver compartment was filled with 125 ml of phosphate buffer 7.4. It was stirred continuously at 600 rpm using Teflon coated magnetic bead and temperature was maintained at 37° ± 0.5 °C throughout the experiment. 5 ml of the receiver fluid was withdrawn at each 1hour interval and replaced with same amount to maintain sink condition. The experiment was buffer withdrawn samples were analyzed for drug content using UV spectrophotometer at 225.4 nm.

#### vi) Skin irritation study:

This study was carried out on healthy albino mice. The animals were divided into 5 groups i.e. Standard, Control, Ethosomal Gel Formulation (G<sub>1</sub>-G<sub>3</sub>). The back skin of area 2 cm<sup>2</sup> was shaved before one day of starting the study. Formalin was used as a standard irritant. The study was carried out for 7 days and each day a formulation was applied. At the end of study, the animals were observed for any Skin irritation like erythema or edema and conducted.

#### vii) Skin permeation studies:

The study was done with minimum animal suffering and least possible animals. After this abdominal skin was excised, washed with phosphate buffer 7.4, carefully cleaned and finally stored at 4°C. The mice skin was then clamped between donor and receiver compartment. The study was carried out as done previously in *in-vitro* release through dialysis membrane.

#### viii) Stability studies:

The stability studies was done on most satisfactory formulation at two different temperature i.e. refrigeration temperature ( $4^{\circ} \pm 2^{\circ}\text{C}$ ) and at room temperature ( $25^{\circ} \pm 2^{\circ}\text{C}$ ) for 6 months. The formulation was kept in a borosilicate container to avoid the interaction between ethosomal formulation and glass of container. The ethosomal formulations were analyzed for physical changes such as color, appearance, entrapment efficiency and *in-vitro* studies<sup>18-22</sup>.

## RESULTS AND DISCUSSIONS:

### Fourier Transform-Infrared Ray Spectroscopy Studies (FT-IR) Studies:

Drug polymer compatibility studies were carried out using *FT-IR* spectroscopy to establish any possible interaction of Gliclazide with the excipients used in the formulation. The *FT-IR* spectra of pure drug, excipients and combination of them were shown in **Figure: 1A, 1B, 1C, 1D**) The data shows that pure drug has 1165, 1347.03, 3263.56, 1600, 3143.97 wave number as major peaks. The results indicated that mixture of pure drug and excipients has no major change in the position of peaks. This shows that there is no possible interaction between drug and excipients.

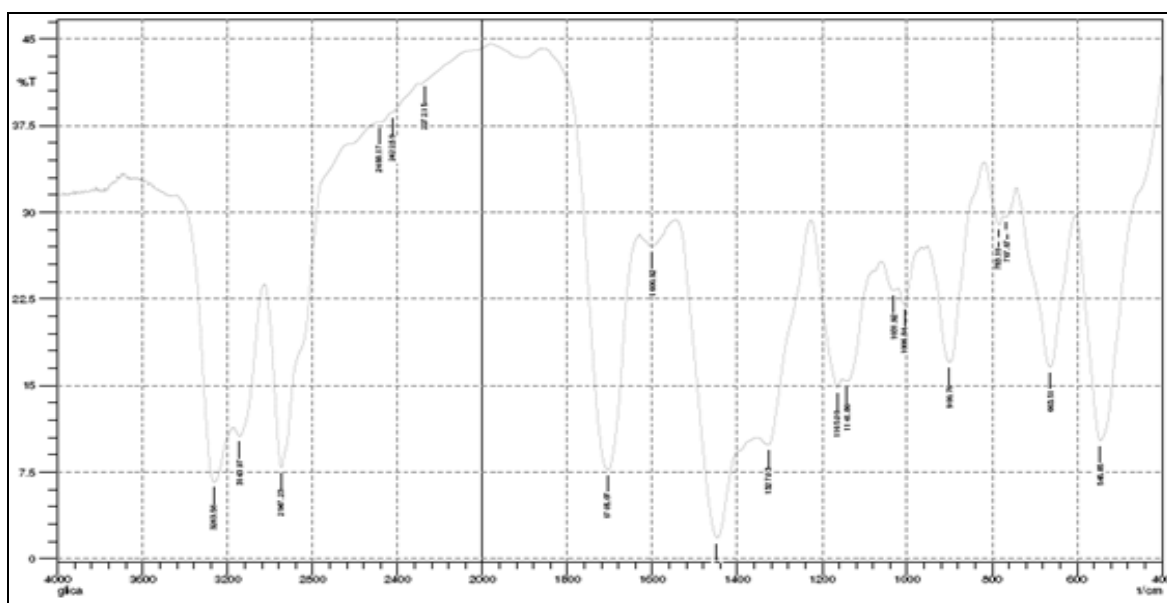


FIGURE: 1A

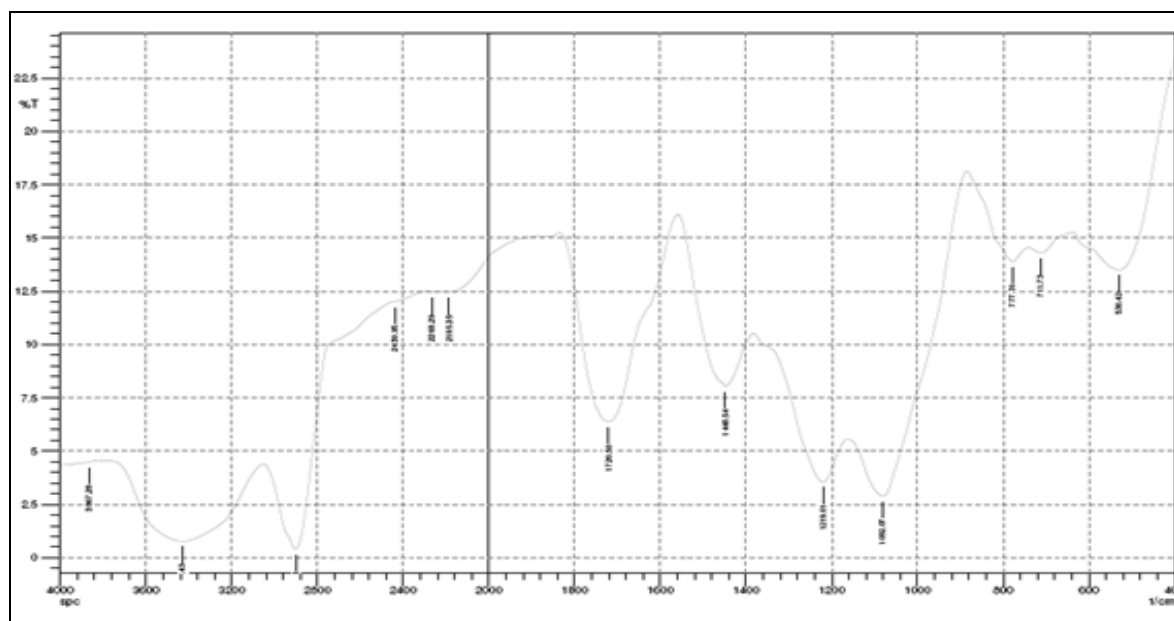


FIGURE:1B

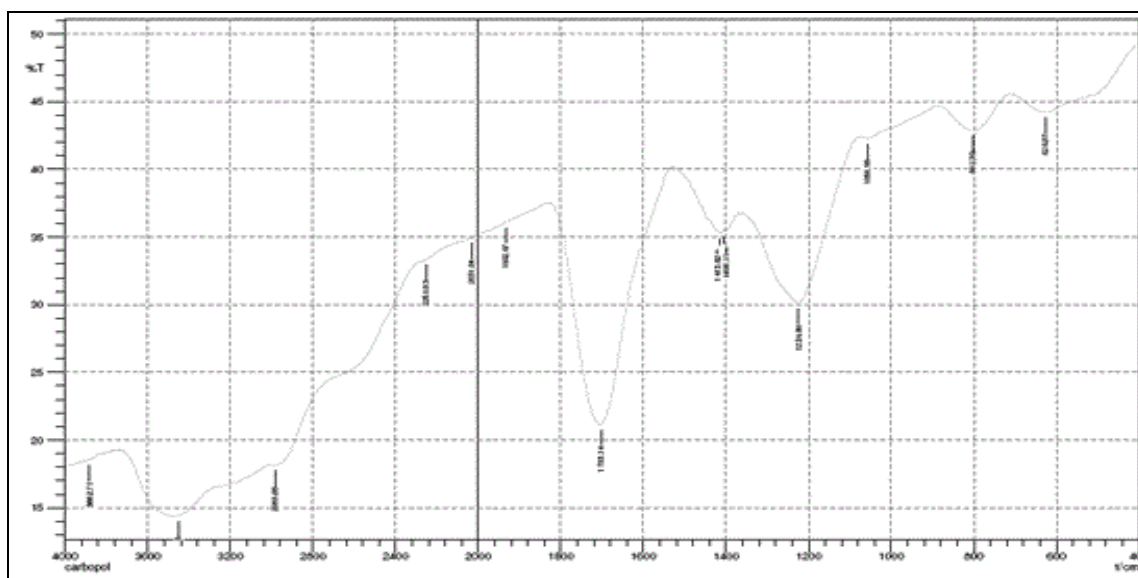


FIGURE: 1C

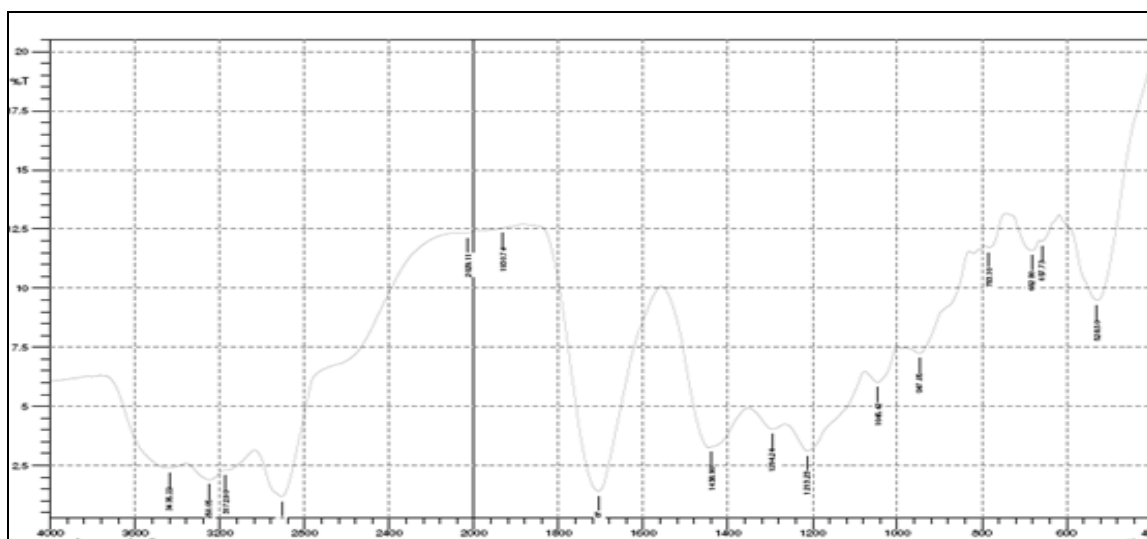


FIGURE: 1D

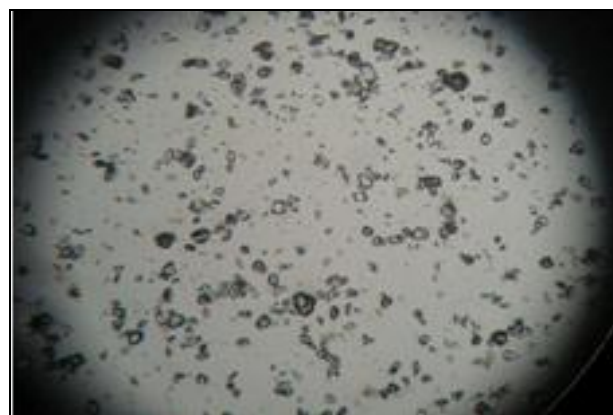
FIG. 1: FT-IR SPECTRA OF 1A) GLICLAZIDE, 1B) PHOSPHOLIPID 1C) CARPOLOL 1D) PHYSICAL MIXTURE

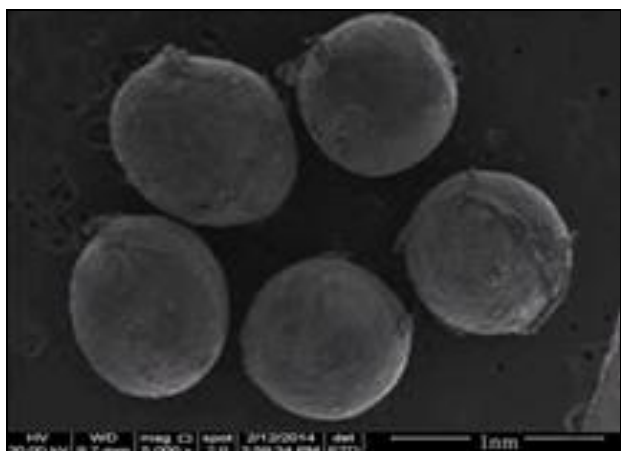
**Vesicle size:**

The vesicle size of ethosomes ranges from 134 to 266 nm. On increasing the concentration of phospholipid from 0.5 to 1% w/w, the size of vesicle was increased and on increasing the concentration of ethanol from 10 to 30% w/v, the size of vesicle decreases. From F<sub>1</sub> to F<sub>6</sub> the size of vesicle increases on increasing the concentration of phospholipid (**Table 4**). From F<sub>1</sub> to F<sub>8</sub> shows that on increasing the concentration of ethanol from 10 to 30% v/v the size of vesicle decreases. This may be due to the formation of a phase with interpenetrating hydrocarbon chain. The decrease in particle size is due to the ethanol, causing a modification of the net charge of the system and some degree of steric stabilization.

**Vesicle shape:**

The vesicle shape of all the ethosomal formulations was found to be spherical with the smooth surface as shown in the **Figure 2**.



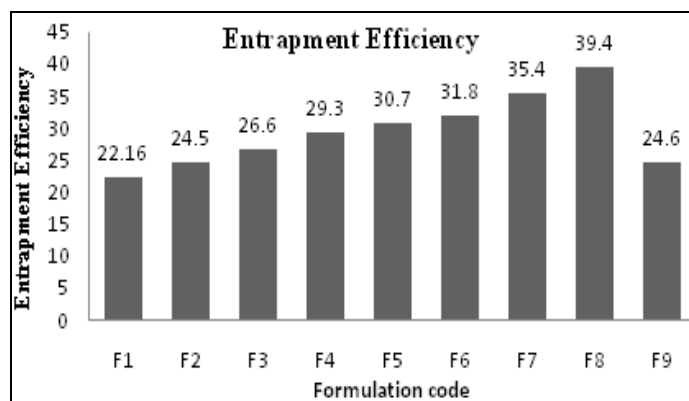


**FIG.2: OPTICAL MICROSCOPE AND SEM FIGURES OF GLICLAZIDE ETHOSOMES**

The turbidity of ethosomal formulation was found to be in the range of  $210 \pm 2.08$  to  $420 \pm 1.02$  NTU. The data shows that on increasing the ethanol concentration from 10 to 30 % v/v the turbidity increases from F<sub>1</sub> to F<sub>9</sub>. The turbidity of F<sub>7</sub> and F<sub>8</sub> were found to be higher than ethosomal formulations (Table 4).

**Entrapment efficiency:**

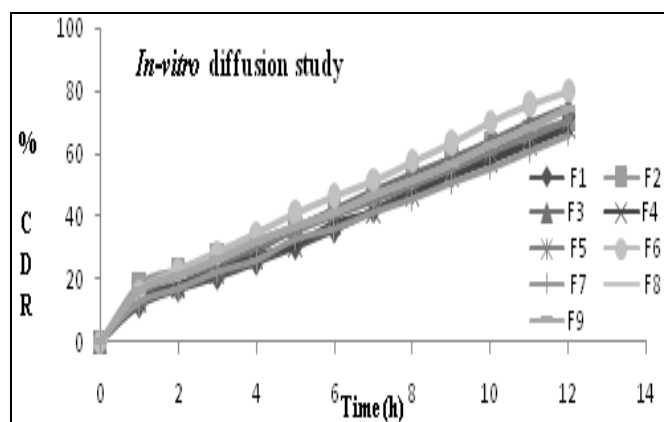
The entrapment efficiency of all the formulations found in the range of  $22.16 \pm 0.12\%$  to  $39.2 \pm 0.2\%$ . The entrapment efficiency of F<sub>8</sub> was found to be maximum whereas in case of F<sub>9</sub> was found to be minimum. Similarly the entrapment efficiency of hydroethanolic solution was found to be less as compared with ethosomal formulation. The different concentration of ethanol and phospholipid on the ethosomal preparation influenced the size of vesicles. The data shows that the entrapment efficiency of vesicle increases on increasing the concentration of ethanol from 10 to 30% v/v and phospholipid concentration 0.5 to 1% w/w (Figure 3).



**FIG.3: ENTRAPMENT EFFICIENCY**

**Drug release profile of ethosomal suspension:**

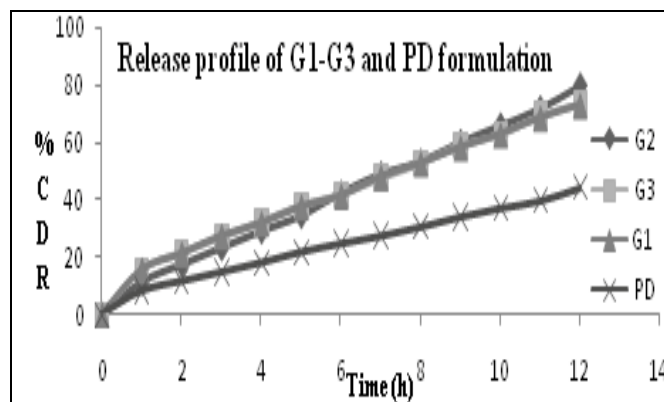
The *in-vitro* drug release of Gliclazide ethosomes was done for 24 hours in Franz diffusion cell in phosphate buffer 7.4 at 37°C. The cumulative percentage of drug release of prepared formulation F<sub>1</sub> to F<sub>9</sub> was in range  $50.87 \pm 0.15$  to  $79.65 \pm 0.56$  respectively at end of 24 hours (Figure 4). Among all the formulations F<sub>6</sub> was found to be the best formulation as drug release was  $79.65 \pm 0.56$  in 24 hrs. There was increase in the amount of drug release with the gradual increase in concentration of ethanol from 10 to 30 % v/v. This may be due to the effect of ethanol, which acts as penetration enhancer.



**FIG. 4: RELEASE PROFILE OF ETHOSOMAL SUSPENSION**

**Release profile of ethosomal gel formulation:**

The Gliclazide ethosomal gel was prepared with three different concentrations of 1, 1.5, 2 % w/w carbopol 934. When the release profile of different ethosomal gel was studied using dialysis membrane and skin of mice, G<sub>2</sub> showed the maximum release up to  $96.06 \pm 0.16\%$  in dialysis membrane and  $79.67 \pm 0.35\%$  in case of mice skin.



**FIG. 5: RELEASE PROFILES OF ETHOSOMAL GEL AND PLAIN DRUG GEL THROUGH MICE SKIN**

In both the cases the results obtained from G<sub>2</sub> formulation was higher than G<sub>1</sub> and G<sub>3</sub> formulation (Figure 5 and 6). Since G<sub>2</sub> showed the maximum release, it was considered favorable for the final development of the formulation.

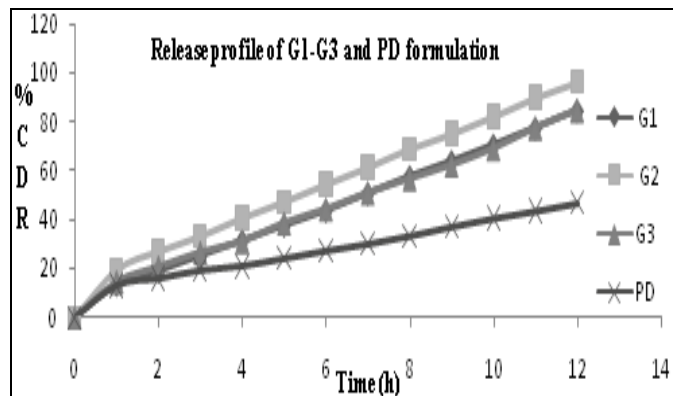


FIG. 6: RELEASE PROFILES OF ETHOSOMAL GEL AND PLAIN DRUG GEL THROUGH DIALYSIS MEMBRANE

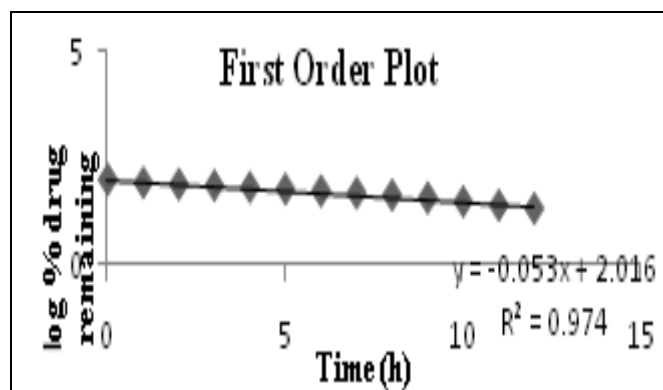


FIG. 7: KINETIC PROFILES SHOWING FIRST ORDER RELEASE

**Skin irritation study:**

In skin irritation study formalin was used a standard irritant and no formulation was used in control group. The results show that skin irritation from ethosomal gel G<sub>1</sub> and G<sub>2</sub> produces the score of 0.5, 1 and 0 at the end of 8 days. Since average score obtained from skin irritation study was obtained less than 2, it can be concluded that ethosomal gel formulation produces no skin irritation (Table 3)

TABLE: 3 SKIN IRRITATION STUDY:

Formulation Code	Average Score		
	Day 1	Day 4	Day 8
Control	0	0	0
Std	0	1.5	3.5
G <sub>1</sub>	0	0	0.5
G <sub>2</sub>	0	0	1
G <sub>3</sub>	0	0	0

TABLE 4: RESULTS SHOWING VESICLE SIZE, TURBIDITY AND ENTRAPMENT EFFICIENCY

Formulation Code	Vesicle Size (nm)	Turbidity (NTU)	Entrapment Efficiency (%)
F <sub>1</sub>	168	210±2.08	2.16±0.17
F <sub>2</sub>	150	260±1.05	4.5±0.2
F <sub>3</sub>	134	280±0.5	6.6±0.47
F <sub>4</sub>	266	230±1.08	9.3±0.3
F <sub>5</sub>	250	251±3.30	0.7±0.30
F <sub>6</sub>	242	265±1.5	1.8±0.15
F <sub>7</sub>	161	409±1.32	5.4±0.41
F <sub>8</sub>	147	424±1.02	9.4±0.2
F <sub>9</sub>	-	250 ±2.04	4.6 ±0.1

**Stability studies:**

The stability study was done on most satisfactory formulation – F<sub>6</sub> at 25° ± 2°C and 4° ± 2°C for period of 6 months and was analyzed for drug release and entrapment efficiency at the end of each month. The residual drug release of F<sub>6</sub> was found to be 80.65 ± 0.35%, 81.45 ± 0.49% and 81.85 ± 0.35, 81.33 ± 0.33, 80.36 ± 0.12, 80.09 ± 0.19 % up to 24 hours respectively at 25° ± 2°C (Figure 8). The drug release was found to be 80.21 ± 0.15 %, 80.05 ± 0.14%, 80.07 ± 0.13, 79.33 ± 0.22, 78.66 ± 0.33 and 78.11 ± 0.21 % respectively at 4° ± 2°C (Figure 9). The entrapment efficiency of drug was found to be 31.8 ± 0.34 %, 32.88 ± 0.20 %, 33.08 ± 0.54 %, 31.58 ± 0.21%, 31.3 ± 0.54 %, 32.5 ± 0.19 %, 31.3 ± 0.65 % at 25°C whereas at 4° C it was found to be 31.8 ± 0.11 %, 31.03 ± 0.12%, 33.08 ± 0.32 % and 31.5 ± 0.23 % and 30.64 ± 0.65 % (Figure 10 and 11). The results showed that there is not much significant difference in entrapment efficiency and *in-vitro* of drug for the period of 6 months.

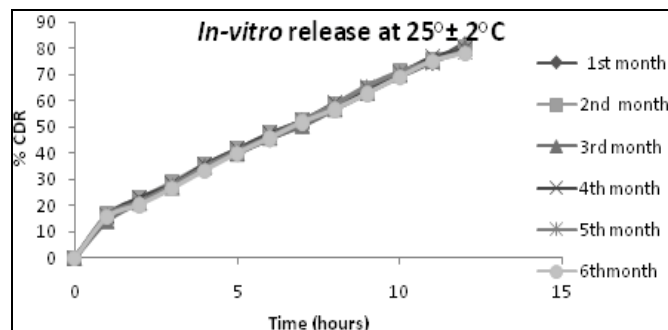


FIG. 8: IN-VITRO DRUG RELEASE AFTER STABILITY STUDY AT 25° ± 2°C

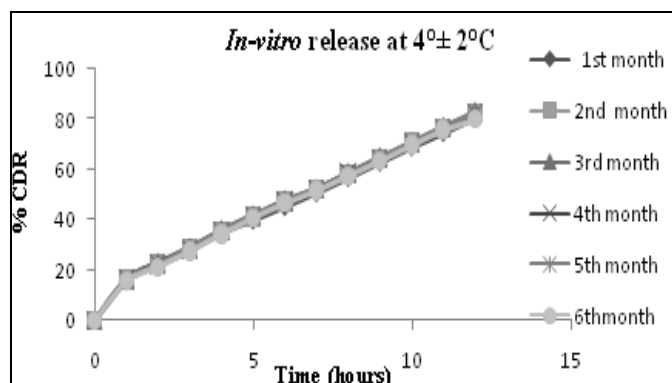


FIG.9: IN-VITRO DRUG RELEASE AFTER STABILITY STUDY AT 4° ± 2°C

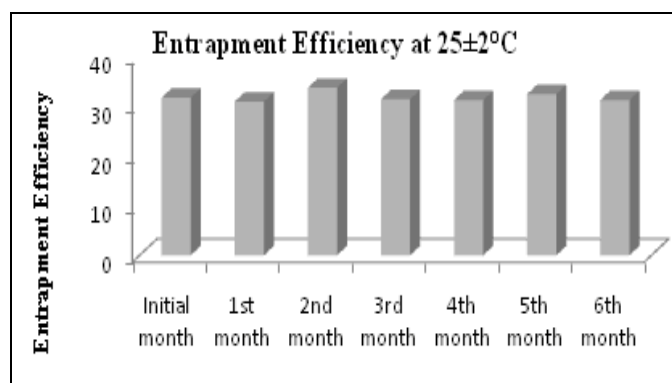


FIG.10: ENTRAPMENT EFFICIENCY AFTER STABILITY STUDY AT 25± 2°C

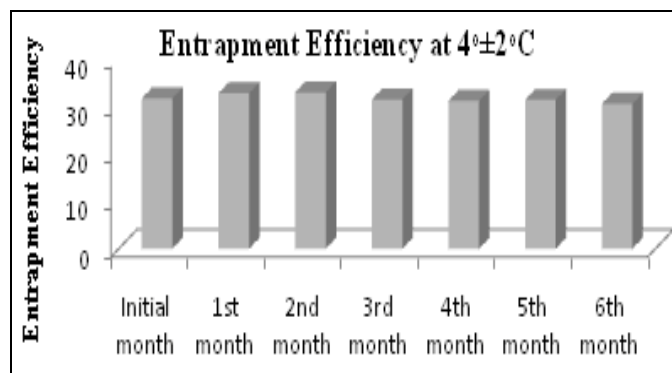


FIG.11: ENTRAPMENT EFFICIENCY AFTER STABILITY STUDY AT 4° ± 2°C

**CONCLUSION:** In this study, total eight ethosomes of Gliclazide by cold method and one formulation of hydroethanolic solution were prepared and evaluated for different parameters. On the basis of different parameters like vesicle shape, vesicle size and entrapment efficiency, F<sub>6</sub> was selected as the best formulation. Thus F<sub>6</sub> was further incorporated to gel using carbopol 934 and carbopol containing 1.5 % w/w showed maximum release. Thus ethosomes were found to be promising candidate for transdermal delivery of Gliclazide. The results showed the potential of

ethosomes of being a safe and very efficient drug carrier for systemic as well as topical delivery of drug.

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