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FORMULATION AND *INVITRO* EVALUATION OF ETHOSOMAL GELS CONTAINING GLIBENCLAMIDE AS THE MODEL DRUG

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ABSTRACT

The process Touitou *et al* (2000) defined was used with little change to prepare various ethosomal formulations with different levels of IPA (20% to 40%) and sonicity. It was simple and reproductible techniques. The prepared and discrete ethosomes have been developed. However, ethosomes are more uniform in size and small, necessary for skin penetration by the process of sonication. When the efficiency of the trap was compared, ethosomes containing 30 percent w/w IPA, which were generated by sonication, displayed the highest value with respect to all others; Therefore, with 30 percent w/w IPA as the best formula for all other aspects, ethosomally provided by sonicity was completed. In all formulations, GF6 demonstrated full release of the drugs in 1,440 min compared to other formulations. The in vitro release decreased with increased concentrations of polymer and copolymer. Centered on the research findings of the drug release process the drug discharge followed the non-fickian diffusion mechanism by formulations and followed the first order kinetics.

KEYWORDS: Ethosomes, Sonication, Transdermal, Entrapment, Stability.

INTRODUCTION

A managed drug supply system has been developed to track drug delivery speeds, maintain therapeutic duration and/or tissue delivery. drug delivery systems were developed.

A convenient four types of controlled drug delivery or modified drug deliveries are divided.

1) Delayed release
2) Sustained release
3) Site-specific targeting
4) Receptor targeting

Controlled delivery can be described more precisely as:[1]

(1) Sustained drug action by sustaining a comparatively stable, efficient body level of prescription drugs with concomitant reduction of undesirable side effects.

2) Spatial location of controlled discharge systems adjacent to or in the tissue of illness, localized drug activity.

3) Targeted action of drugs to supply the medication to a specific target cell type using carriers or chemical derivatives.

4) Have a prescription release mechanism based physiologically and therapically. In other words, physiological and clinical requirements of the body decide the volume and the rate of release of drugs".[2]

"Usually, a regulated method for the delivery of drugs is built in particular to supply the medication. Blood levels are kept stable and efficient for a time when the machine is distributing medication. Regulated drug entry typically leads to significantly constant active ingredient blood levels compared to uncontrolled fluctuations when several doses of rapid release are administered to patients for the traditional dosage types.

Currently, an oral route is the most common method of drug delivery. While the benefit of ease of administration is noteworthy, it also has significant disadvantages, namely poor bioavailability, due to metabolism in the first place and a propensity to generate high and low blood spikes, leading to a need for high or regular dosing, which can be both prohibitive as well as inconvenient".[2]

"The development of an emergent drug delivery system, enhancing the therapeutic effectiveness and drug protection, by making spatial and temporary placements within the body more reliable (i.e. precise site), reduces both size and number of doses, is required in order to solve these problems. New drug delivery schemes are also necessary in order to supply the site without any major immunosupply or biological inactivation with novel genetically engineered medicinal products (i.e. peptides, proteins). In addition to these benefits, pharmaceutical firms understand that the idea and technologies of a managed drug delivery system and the cost associated with getting new drug companies into the market are feasible for repatenting successable drugs. Transdermal delivery of medicinal substances through

the skin for systemic effects was one of the most commonly used methods.[2]

"The present study is equipped with two different polymer combinations: E RS100 and HPMC E 15, E RL 100 with HPMC E 15, to establish a suitable matry style transdermal drug delivery systems for Ketorolac. The acrylic acid matrices E RL100 and E RS 100 are used to manufacture drug polymer matrix films, which are stated to be compatible with several drugs. Penetration changes that can help increase drug permeation partitioning[3]. Various D-Limonene penetration enhancers, Oleic and their effects on drug permeation, were used at various concentrations in the study".

DRUG DELIVERY SYSTEMS OF TRANSDERMAL

"Transdermal drug delivery systems are topical medicines in the form of patches delivering medicines for a predetermined systemic impact And controlled pace. - And controlled rate.

A transdermal drug delivery system, 'which can be of an active or passive nature, is an alternate medication path. These devices can be administered through the skin barrier to pharmaceutical products. A medicine is administered to the skin of a patch at a reasonably high dose over a long period of time. The drug reaches the bloodstream directly through the skin through a dissemination process. The substance is still diffused in the blood" for a long period of time because the patch is high and the blood concentrations are low, and the drug persists in blood.

Advantages[4-8]

The transdermal route is a "interesting option," since it is a realistic and secure transdermal route. The beneficial characteristics of drug delivery through the skin are systemic consequences.

1. "Avoidance of first pass metabolism.
2. Avoidance of gastro intestinal incompatibility.
3. Predictable and extended duration of activity.
4. Minimizing undesirable side effects.
5. Provides utilization of drugs with short biological half-lives.
6. Improving physiological and pharmacological response.
7. Avoiding the fluctuation in drug levels.
8. Avoiding inter and intra patient variations.
9. Maintain plasma concentration of potent drugs.
10. Termination of therapy is easy at any point of time.
11. Greater patient compliance due to elimination of multiple dosing profile.
12. Ability to deliver drug more selectively to a specific site.
13. Provide suitability for self-administration and enhance" therapeutic efficacy.

Mechanism of penetration

"While speculation still concerns the exact process of medicinal supply by ethosomes, a combination of processes probably contributes to the improvement of the effect. The multi-layer stratum corneum lipid is tightly packaged and highly conformational at physiological temperature. The high ethanol content makes ethosomes special, since ethanol is known to disrupt the organization of the bilayer of the skin lipid. It thus enables the vesicles to penetrate a streatum corneum when integrated into a vesicles membrane. The lipid membrane is packed less securely than traditional vesicles due to its high ethanol content, but has an equal strength that allows a structure that can be more malt-free and allows more mobility, squeezing through small squares, such as openings created to disrupt the lipid stratum corneum".[9]

"Ethanol interacts with lipid molecules in the hard group polar region, which decreases the stiffness of the corneal stratum lipids and increases their fluidity. The intercalation of ethanol into the environment of the polar head group will lead to increased membrane permeability. The ethosome itself can interact with the stratum corneal barrier as well as the effect of ethanol upon the layered corneal structure".[10]

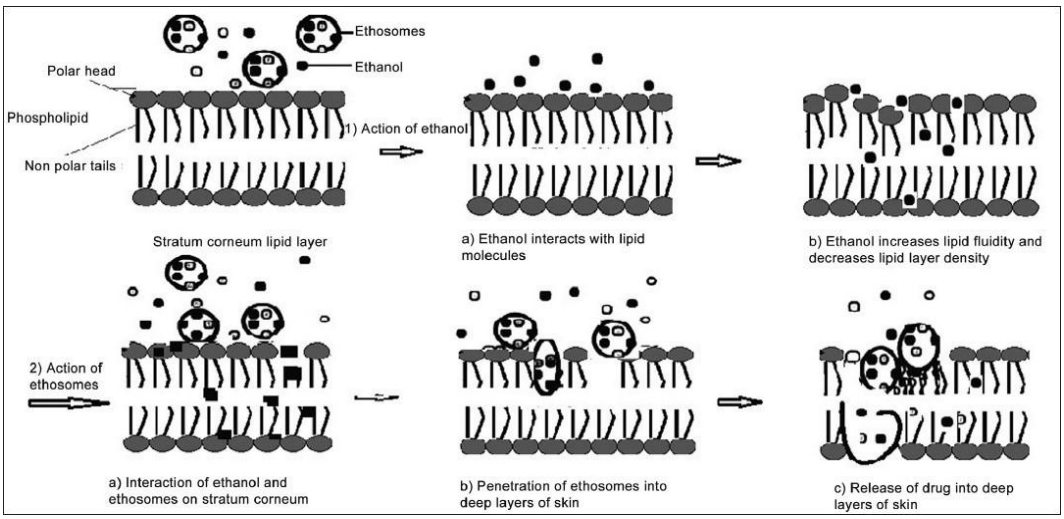

Figure 01: Proposed model of skin delivery ethosomal system.

The "interdigital and malleable vesicle of ethosomes will trace paths in the distorted stratum. The higher positive zeta-potential of the drugs can increase the skin attachment of the vesicles in the case of drug encapsulation ethosomes. The ethosomal system was shown to be highly efficient carriers for increased drug use in skin while encapsulated medication in classic liposomes remained primarily at the skin's surface. This method is a promising candidate for transdermal supply of the medication because of its efficient supply along with the long-term stability of the ethosomes.[11]

Planning Preparation

"The Touitou *et al*. reports that the ethosomal system can be produced with soybean phosphotidyl choline 2 – 5 percent, 20 – 50 percent w/w, and medications and waters, at 100 percent w/w. "Ethosomal formulation and preparation is the result of Touitou *et al*. Ethanol dissolves 90 and medication for the preparation of ethosomes phospholipid. As a slender stream with a steady mix at 700 rpm, double distilled water was added slowly into a well settled bottle. For another 5 minutes, mixing has been continued. During the preparation, the machine was kept at 30 °C and then stored cold".[12]

Table 01: Different additives used in ethosomal formulation.

Class	Example	Uses
Phospholipid	"Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline"[11]	Vesicles forming component
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	"For providing the softness for vesicle membrane As a penetration enhancer"[12]
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	"Rhodamine-123 Rhodamine red FluoresceneIsothiocynate (FITC) 6- Carboxy fluorescence"[12]	For characterization study
Vehicle	Carbopol 934	As a gel former

GLIBENCLAMIDE

Glibenclamide is a non-insulin-dependent diabetes mellitus anti hyperglycemic oral agent (NIDDM). He is a member of the insulin secretagogue sulfonylurea class that stimulates the release of insulin by β cells in the pancreas. The release of basal insulin and meal-stimulated insulin by sulfonylurea increases.

Blood glucose decreases acutely by stimulation of the release of Pancreas' insulin, an impact dependent on the active beta cells of pancreas. Glibenclamide is an antidiabetic sulphonylurea agent of the second century. The blood glucose reduction effect continues in the chronic administration of type II diabetic patients despite a steady decrease in the secretive insulin response to the medication. The mechanism of action of oral hypoglycemic sulfonyl urea can be impaired by extra pancreas impact. Glibenclamide and metformin combinations may have synergistic effects as both agents increase the tolerance of glucose by different but complementary mechanisms. Glibenclamide causes mild diuresis by enhanced renal free water clearance, besides its blood glucose reductions. Glibenclamide is twice as powerful as the glipizide of second generation.

AIM AND OBJECTIVE

The purpose of the present investigation is aimed at

To prepare and evaluate and Glibenclamide ethosomes containing different concentration of ethanol and phospholipids by sonication for size reduction of vesicles.

The designated ethosomes of Glibenclamide are characterized by

- Size and shape
- Entrapment effectiveness
- Study of release

The influence of sonication was also investigated on the characteristics of the ethosomes of Glibenclamide.

PLAN OF WORK

- To formulate ethosomal gel.
- To characterize the prepared formulation using cold method.
- To carry out different criteria of assessment, including vesicular form and surface morphology, vesicular duration, drug quality, efficiency of trapping.
- To carry out *in vitro* drug diffusion study of ethosomal gel.

- **Preformulation studies**
  - API Characterization.
  - Studies into solubility.
  - Compatibility reports of Drug Excipients.
- **Construction of Calibration curve.**
- **Formulation Development.**
- **Characterization of ethosomal gel.**

Size and shape analysis

Entrapment efficiency
pH
Spreadability
Drug content and content uniformity
Drug release study
Invitro release kinetics

- **Stability studies** (at 30ºC / 75 % RH and 40ºC / 75 % RH)

NEED FOR THE STUDY

The increased need to supply patients with less adverse reactions and better compliance with medication effectively has intensified the pace at which new medicines have been developed. The transdermal route is expanded to include, separately from oral, innovative drug delivery technology. The ability to improve transdermal permeation can be useful when complications are associated with oral administration of medicine.

Therefore, the route of administration needs to be changed for enhanced drug absorption. The transdermal administration course may be more fitting.

Glibincamide transdermal penetration cannot be increased by niosomes or liposomes due to their dimensions and their rigid lipid layer characteristics. In 2004, the lipid vesicles were used to increase the amount of substrate, thus increasing the penetration of the compound from the drug. As a result of the innovation, the lipid vesicles were formed. Glibenclamide was influenced to enhance skin penetration. The compound was stabilized in the vesicles thus stabilizing the compound for an extended duration. In addition, the overstated effect of the vesicles on cGMP led to the reduction of dose. As a result, the drugs reduced the adverse effects of the drugs. Instead of the instance that the vesicles released the chemical suddenly, the compound was formulated slowly for prolonged action. In addition, the vesicles reduced the fluctuation in the blood levels of the drugs. Since the size of the vesicles was suitable, the overall results of treatment on the whole varied. The results caused less impact on the breakouts. Therefore, the patients were able to adapt the changes in the administration.

MATERIALS AND METHODS

Glibenclamide was obtained as gift sample from Chandra labs Pvt. Ltd, Hyderabad, Soya lecithin Mylan Chemicals, Propylene glycol Avantor chemicals, Methanol, Mark chemical Cholesterol, Virat lab (Mumbai), Carbopol-940 Srini Chemicals, Tri ethanol amine, Avantor chemicals, Ultrapure water Mark chemical reagents etc

METHODOLOGY

PRE-FORMULATION STUDIES[13]

"Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational development of dosage forms.

PREPARATION OF GLIBENCLAMIDE ETHOSOMES (BY COLD METHOD)

Preparation of Glibenclamide ethosomes was followed by method suggested by Touitou *et al*. with little modification.[7]

The "ethosomal system of Glibenclamide comprised of 2-6 % phospholipids, 20-40 % isopropyl alcohol, 10 % of propylene glycol,0.005g of cholesterol and aqueous phase to 100 % w/w. Glibenclamide0.1 g was dissolved in IPA in a covered vessel at room temperature by vigorous stirring. Propylene glycol was added during stirring. This mixture was heated to 30^0 in a separate vessel and was added to the mixture drop wise in the center of the vessel, which was stirred for 5min at 700rpm in a covered vessel the vesicle size of ethosomal formulation can be decreased to desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration[31].Ethosomes were formed spontaneously by the process".[14]

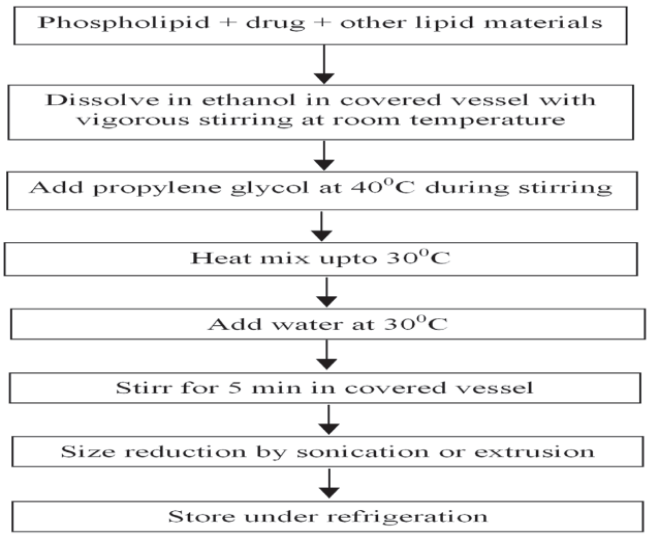

Figure 02: Cold method for the preparation of ethosomes.

Table -02: Composition of different ethosomal formulations.

Ethosomal formulation	Lecithin (Soya lecithin%)	IPA(%)	Propylene glycol (%)	Glibenclamide (g)	Cholesterol (g)	Water
GF_1	2ml	20ml	5ml	0.1g	0.005g	100ml
GF_2	4ml	20ml	5ml	0.1g	0.005g	100ml
GF_3	6ml	20ml	5ml	0.1g	0.005g	100ml
GF_4	2ml	30ml	5ml	0.1g	0.005g	100ml
GF_5	4ml	30ml	5ml	0.1g	0.005g	100ml
GF_6	6ml	30ml	5ml	0.1g	0.005g	100ml
GF_7	2ml	40ml	5ml	0.1g	0.005g	100ml
GF8	4ml	40ml	5ml	0.1g	0.005g	100ml
GF9	6ml	40ml	5ml	0.1g	0.005g	100ml

Preparation of Glibenclamide ethosomal gel.

The best achieved suspension of ethosomal vesicles was introduced into carbopol gel (1%, 1.5%, 2% w/w). The specified volume of carbopol 934 powder was slowly applied to ultrapure water and held for 20 minutes at 1000c. It was applied dropwise to triethanolamine. Sufficient quantity of formula (GF-2) comprising glibenclamide (1.5 percent w/w was then introduced into gel-base. Water q.s was added with other continuous stirring formulations before homogeneous formulation was obtained (G-1, G-2 and G-3). glibenclamide containing gel was prepared using 1.5 by similar process.

Table 03: Composition of different ethosomal gel formulation.

Gel formulation	Glibenclamide ethosomal suspension(ml)	Carbopol 940(%)	Triethanolamine (ml)	Phosphate buffer (pH 6.8)
G-1	20ml	0.5	0.5	q.s
G-2	20ml	1	0.5	q.s
G-3	20ml	1.5	0.5	q.s

CHARACTERIZATION OF ETHOSOMES

SIZE AND SHAPE ANALYSIS

To determine the average size of the ethosomes, microscopic analysis was conducted. "In order to observe individual vesicles, a sample of ethosomes was sufficiently diluted with distilled water and a drop of diluted suspension was mounted on a glass slide covered with a cover slip and examined under a microscope (magnification 15 X 45 X). The diameters of 150 vesicles were randomly calculated using a calibrated stage micrometre eyepiece micrometre. The method used to measure the average diameter was".[15]

Average diameter = nd / n

n = number of vesicles

d = diameter of vesicles

The vesicle size was diminished by sonication. Although the vesicular dimension of these vesicles could not be measured with a magnification of 15 X 45 X using a microscopic process. Sonicated vesicles were then examined under a special microscope linked to software and photomicrographs were taken under magnifications of 400 and 800. For size analysis, more selected photomicrographs were analyzed using special "particle size analysis" software developed by BIOVIS. This particular programme functions on photomicrograph images of normal dimensional measurements.

SCANNING ELECTRON MICROSCOPY

Determination of surface morphology (roundness, smoothness and formation of aggregates) of ethosomal gel with polymer was carried out by scanning electron microscopy (SEM).

***In-Vitro* RELEASE STUDIES**

DRUG RELEASE STUDY FROM DIALYSIS MEMBRANE OF GLIBENCLAMIDE

Glibenclamide "skin permeation from ethosomal formulation was tested using open-ended diffusion cells precisely developed according to literacy in our laboratory"[16] The successful permeation area was 2.4 cm and 200 ml for the diffusion cell and receptor cell number, respectively. At 37 ± 0.5 °C.2 the temperature was preserved.

"The receptor compartment held 200 ml of pH 6.8 buffer and was continuously stirring at 100 rpm by means of a magnetic stirrer. Between the donor and the receptor compartments, ready dialysis was placed. Ethosomal formulation was added to the dialysis membrane and the material of the diffusion cell was placed under continuous stirring, during which 5 ml of samples were extracted at fixed time intervals from the receptor compartment of the diffusion cell and analysed by spectrometric approach at 229 nm following sufficient dilution. The receptor process was replenished directly with the same fresh pH6.8 buffer volume. For opioid release trials, triplicate experiments were performed".[3]

In-vitro release kinetics[17]

A series of "kinetic models were used to describe the in vitro release effects and analyse the way that they

worked out. Eq. (2) determines the mechanisms by which the release rate of the pharmaceuticals depends on its concentration. Eq. (3) determines the exhaust from the unit where the exhaust rate depends on the concentration. Higuchi (1963) explains the release of time dependent drugs and the distribution of insoluble matrix from a square root based on Ficki".

The "results of the in vitro release profile obtained for all the formulations are defined in the following three data treatment modes: all release regulation, low and high release scenarios.

- A zero-order kinetic model of cumulative drug release percentage versus time.
- We plotted the course of First-Order-Log cumulative percent for our therapy versus time.
- Cumulative percent drug release d versus square root of time, Hikuichi's model.
- The Korsmeyer Equation/Peppa Model- Log cumulative drug release percentage versus log time".[18]

Table 04: Developing a new diffusion model for cylindrical form.

"S.No	Diffusion	Exponent (n) Overall solute Diffusion mechanism
1.	0.45	Fickian diffusion
2.	0.45<n<0.89	Anomalous (non-Fickian) diffusion
3.	0.89	Case-II transport
4.	n>0.89	Super case-II transport"[19]

STABILITY STUDIES

The stability analysis for Glibenclamide ethosomal preparation was performed at two separate temperatures, i.e. the cooling temperature (4 ± 2 °C) at room temperature (27 ± 2 °C) for 8 weeks (as per ICH guidelines). The formulation was subjected to a stability analysis and placed in a borosilicate bottle to prevent any contact between the ethosomal preparation and the container glass that could impact the findings.

- **In-vitro stability release study**

Drug stability and vesicle stability are the key determinants of formulation stability, experiments have been carried out to determine the overall drug content at room temperature (27 ± 2 ° C) and cooling temperature (4 ± 2 ° C). Samples were collected every 2 weeks and absorption was seen at 229 nm in the U.V spectrometer.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Table 05: Table showing the description of Glibenclamide (API)

Test	Description
Colour	A white crystalline odorless powder

Result: The results were decided according to requirements**.**

- **Solubility**

These studies were carried out in conjunction with the protocol and the findings are shown in the following table.

Table 06: Solubility of Glibenclamide (API) in various solvents.

SOLVENTS	SOLUBILITY
Water	Insoluble
Methanol	Soluble
Alcohol	Soluble
Acetonitrile	soluble

- **Melting Point**

This test is performed as per procedure and the result was illustrated in the following table.

Table 07: Showing the point of melting API's.

Material	Melting Point
Glibenclamide	169^0c

Result: The result has been found to be minimal.

GLIBENCLAMIDE CALIBRATION CURVE IN pH 6.8 PHOSPHATE BUFFER

Table 08: Concentration and absorbances.

S.NO	Concentration	Absorbances
1	0	0
2	5	0.15
3	10	0.291
4	15	0.462
5	20	0.623
6	25	0.765

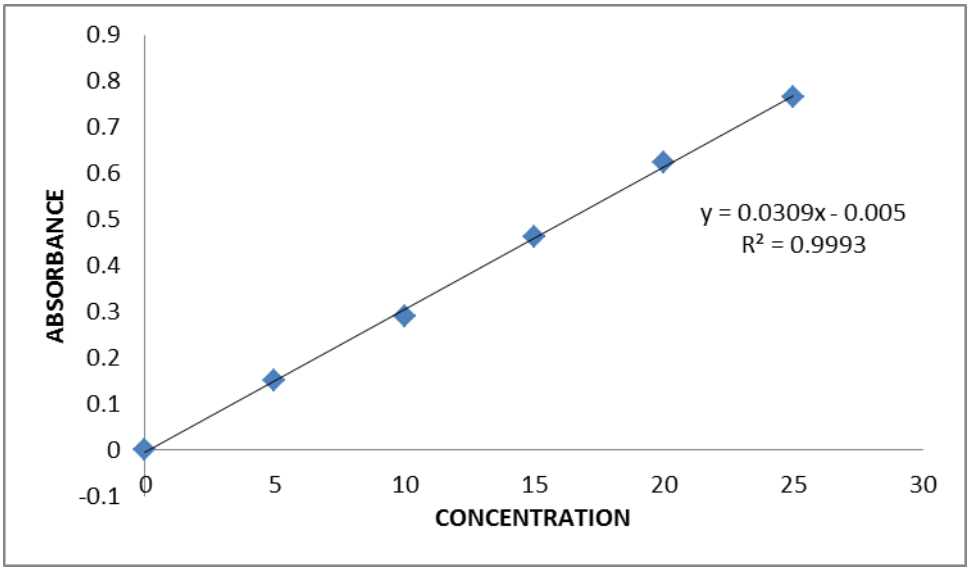

Figure 03: Calibration curve of Glibenclamide graph.

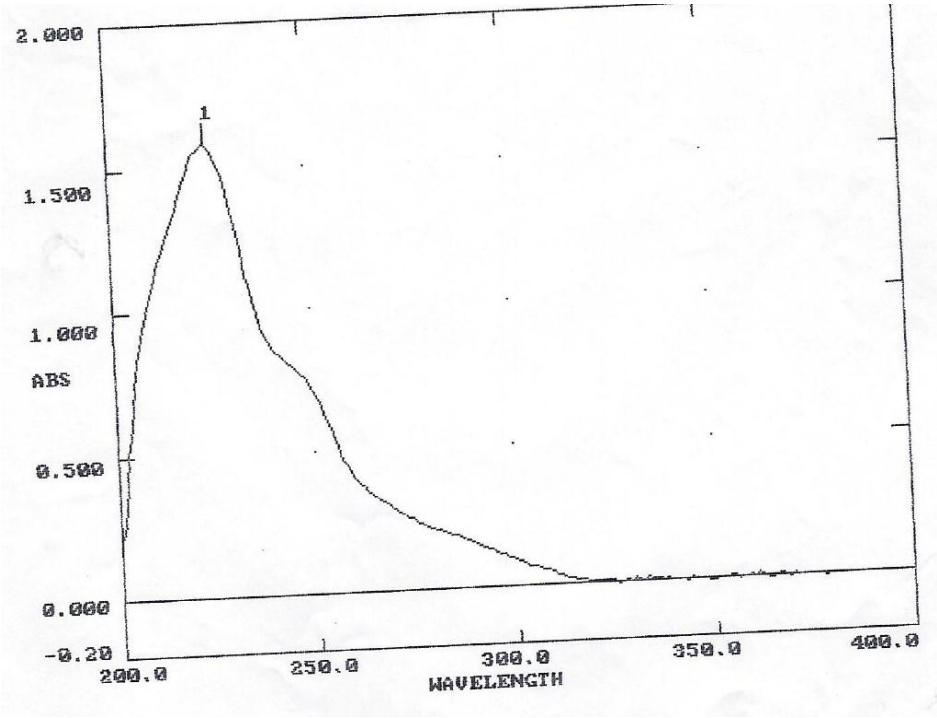

Figure 04: UV sprctrum for Glibenclamide at 229nm.

FTIR STUDIES

In functional peaks and in functional classes, IRspectra were compared and checked for improvement. It is evident from the continuum that there is no correlation between the selected carriers, drugs and mixtures. Consequently, without any mutual interaction, the chosen carrier was found to be compatible with those selected carriers.

FTIR experiments were performed to illustrate the safety of the drug with several excipients.

ETHOSOMAS CHARACTERIZATION

Although the physical characterization of the dose form is directed at physical honesty, the data have been clustered together at one location. Discussion of the results listed under the same heading for the formulation of ethosomes.

SIZE AND SHAPE ANALYSIS

Microscopical inspection was conducted under distinct magnification to imagine the vesicular shape, lamellarity and the size of ethosomal preparations.

SCANNING ELECTRON MICROSCOPE (SEM)

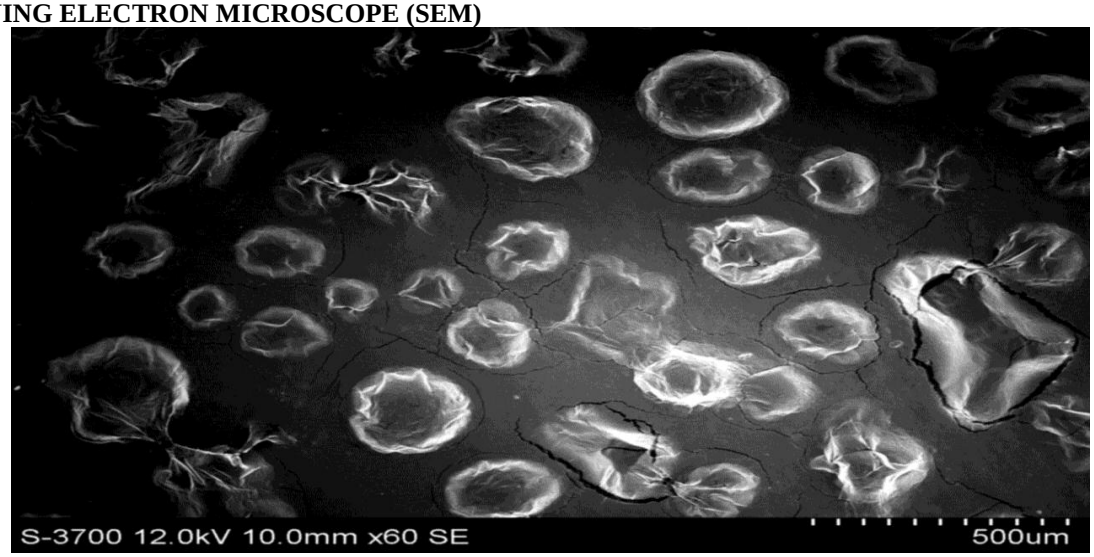

Figure 05: Scanning electron microscope image.

ETHOSOMAL GEL ENTRAPMENT EFFICIENCY

Ultracentrifugation explored the potential of vesicles for drug trapping until the existence of bilayer vesicles was established in the ethosomal method. The method used to extract drug-containing vesicles and the untrapped or free drug used for the evaluation of trapping performance was ultra-centrifugation.

Table 09: Drug entrapment efficiency of Glibenclamide.

Formulation code	Entrapment efficiency (%)
GF1	72.1
GF2	76.5
GF3	78.2
GF4	77.1
GF5	81.4
GF6	84.8
GF7	81.9
GF8	82.7
GF9	86.8

As calculated by ultracentrifugation, the overall capture efficiency of ethosomal vesicles was 86.8 percent for Glibenclamide ethosomal formulations containing 40 percent IPA (GF9). As the IPA concentration increased from 20 percent to 40 percent w/w, the capture efficiency increased and the ethanol concentration increased more (> 40 percent w/w). Four percent phospholipid trapping results also indicate optimum trapping efficiency concentrations and, subsequently, higher or decreased phospholipid concentrations lower trapping efficiency. The findings further validate these findings of Jain NK *et al*., 144 The efficacy of ethosomal formulations in capture is substantially different and is stated in the table.

The potential decrease in vesicle size may be due to an improvement in entrapment performance. The negative effect on the vesicle, which is greater in size during ultra-centrifugation. The more uniform lamellae, smaller vesicles and uniform scale are given by Sonication which can also contribute to improved stabilization during ultracentrifuge and lower vesicular disruption.

EVALUATION OF ETHOSOMAL GEL

Table 10: Organoleptic characteristics of ethosomal gel.

Organoleptic Characteristics:	Color: brownish-yellow Greasiness: Non greasy Grittiness: Free from grittiness Ease of application: Easily/smoothly applied Skin irritation: No skin irritation
Washability:	Easily washable without leaving any residue on the surface of the skin.

Physical appearance

Formulation code	Color	Homogeneity	Consistency	Phase separation
GF1	Creamy white	Homogenous	Smooth	-
GF2	Creamy white	Homogenous	Smooth	-
GF3	Creamy white	Homogenous	Smooth	-
GF4	Creamy white	Homogenous	Smooth	-
GF5	Creamy white	Homogenous	Smooth	-
GF6	Creamy white	Homogenous	Smooth	-
GF7	Creamy white	Homogenous	Smooth	-
GF8	Creamy white	Homogenous	Smooth	-
GF8	Creamy white	Homogenous	Smooth	-

Spreadability studies

S.no	Formulation code	Spreadability (g.cm/sec)
1	GF1	14.28
2	GF2	16.42
3	GF3	13.74
4	GF4	15.26
5	GF5	16.67
6	GF6	17.81
7	GF7	18.54
8	GF8	15.49
9	GF9	18.76

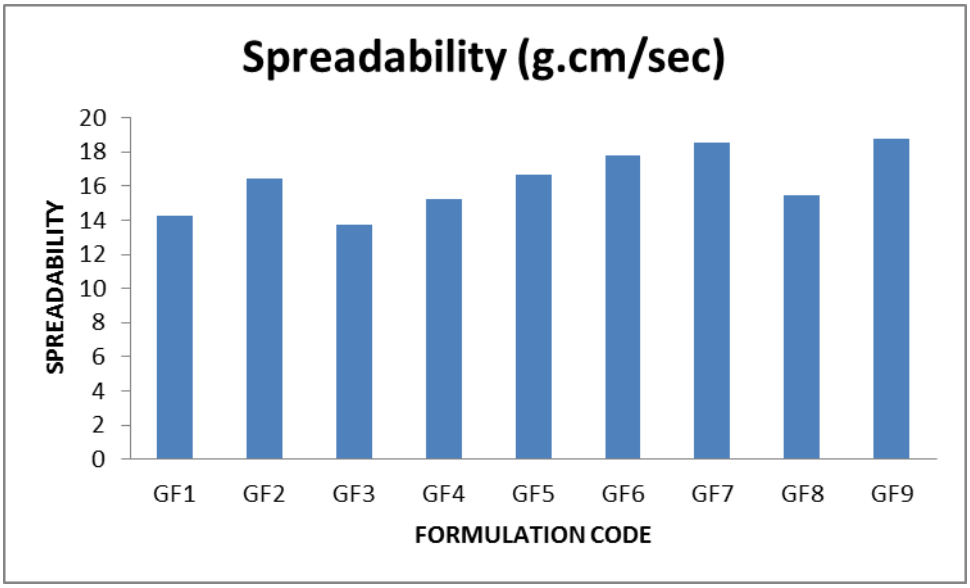

Figure 06: Spreadability graph for GF1-GF9.

Table 11: Rheological studies (for 10rpm spindle 6).

S.no	Formulation code	Viscosity (cps)
1	GF1	1815
2	GF2	1824
3	GF3	2046
4	GF4	2132
5	GF5	1674
6	GF6	1679
7	GF7	1670
8	GF8	1674
9	GF9	1672

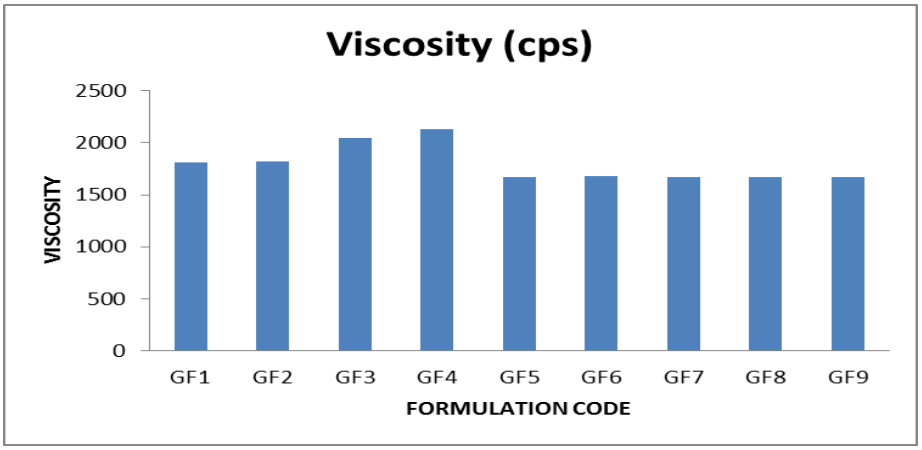

Figure 07: Viscosity Graph for GF1-GF9.

The pH of gels was measured by using electrode based digital pH meter.

Table 12: P^H measurements of Ethosomal gel.

The pH values for all formulations were in the range of 5.9 to 6.6

Formulation code	pH
GF1	5.9
GF2	6.3
GF3	6.8
GF4	5.9
GF5	6.4
GF6	6.6
GF7	6.5
GF8	6.6
GF9	6.8

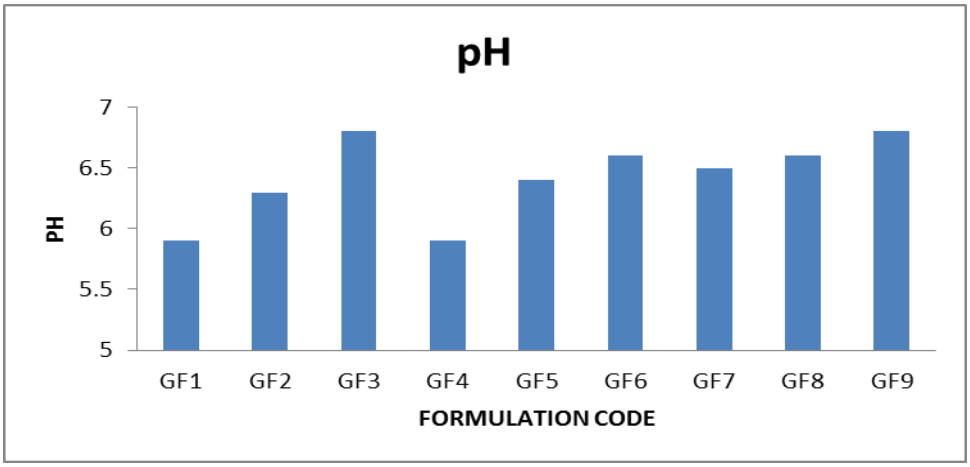

Figure 08: Surface PH graph for GF1-GF9.

Table 13: Drug content for Glibenclamide.

Formulation code	Drug content (%)
GF1	95.2
GF2	97.4
GF3	98.6
GF4	96.5
GF5	97.1
GF6	98.4
GF7	94.8
GF8	96.9
GF9	98.4

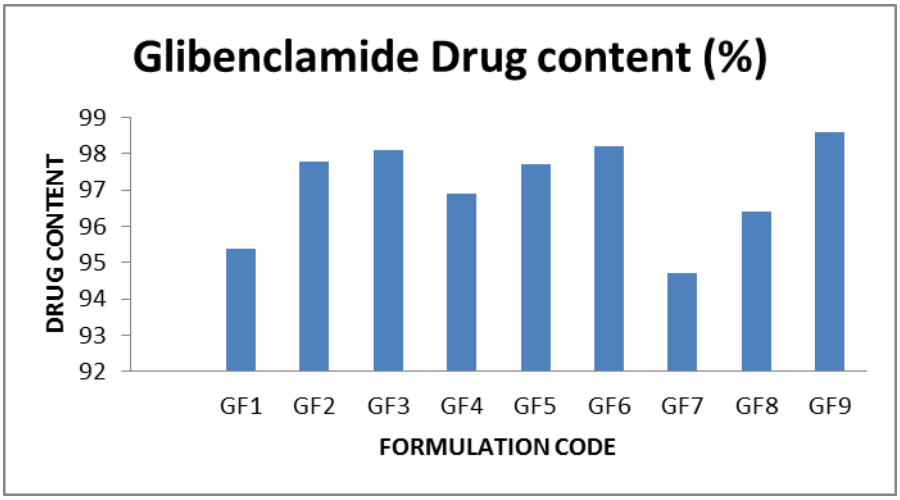

Figure 09: Drug Content Graph For GF1-GF9.

Vesicle size

Vesicle size of the ethosome was measured by zeta sizer. The size of the vesicle was found to be 430nm with a pdi of 0.168.

Resultssize(d.nm):	**%Intensity**	**Width(d.nm)**		
Z- AVERAGE (D.NM): 430	**Peak1: 426.5**	**100**	**104.2**	
PdI: 0.168	**Peak2:--**	**--**	**--**	
Intercept: 0.96	**Peak3:--**	**--**	**--**	
Result quality: good				

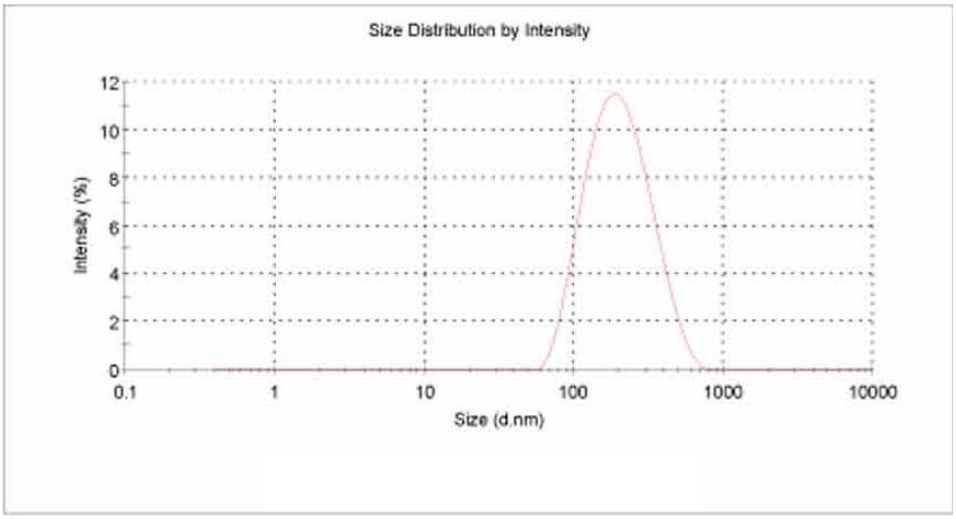

Table 14: Cumulative proportion of cumulative Glibenclamide in vitro ethosomes.

Time (hrs)	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF8	GF9
0.08	32.4	12.8	6.57	2.16	6.24	7.24	6.6	5.12	4.42
0.16	47.2	29.14	16.29	8.24	13.59	15.85	11.08	12.46	9.18
0.25	57.40	32.21	29.04	20.67	26.14	30.22	27.2	24.25	20.35
0.5	69.24	51.24	36.02	26.42	37.61	42.64	34.04	31.24	28.62
1	72.46	67.16	62.1	37.04	43.66	54.26	39.7	35.14	34.59
2	84.5	82.17	74.3	44.8	55.72	61.47	52.4	48.75	46.24
4	100.4	90.52	89.3	55.6	64.27	67.45	60.6	56.52	57.64
6		100.6	100.9	60.74	69.54	74.40	67.7	65.14	61.22
12				69.12	77.25	83.12	79.5	72.26	67.12
24				77.69	86.14	96.48	88.11	78.4	73.7

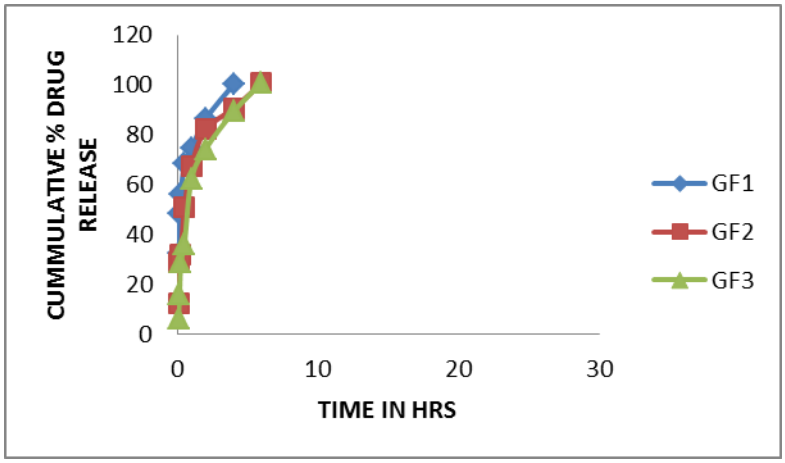

Figure 10:Ethosomes containing Glibenclamide dissolution profile for formulations GF1-GF3.

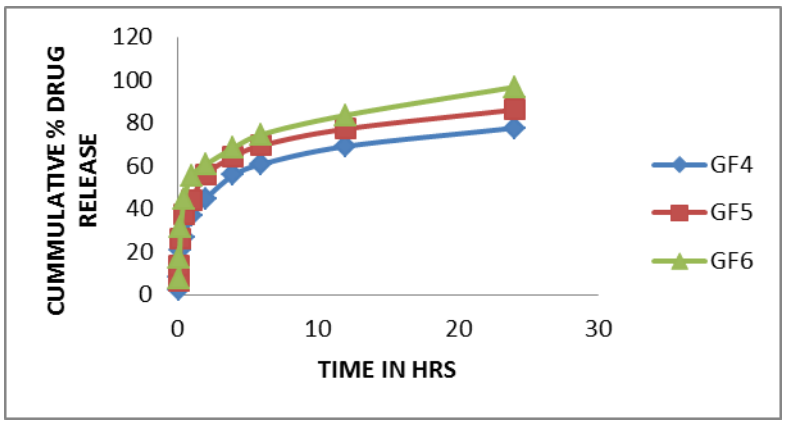

Figure 11: Ethosomes containing Glibenclamide dissolution profile for formulations GF4-GF6.

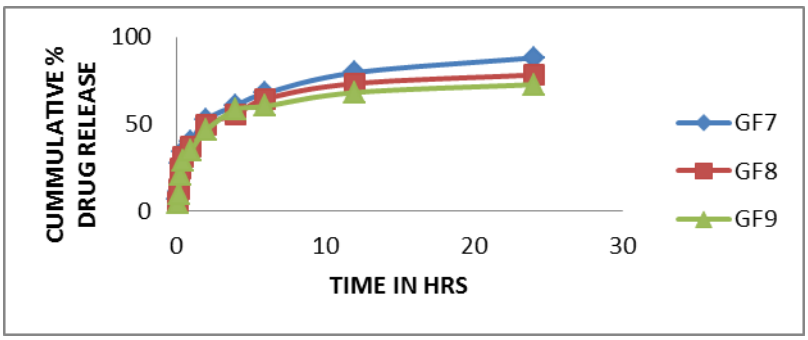

Figure 12: Ethosomes containing Glibenclamide dissolution profile for formulations GF7-GF9.

ETHOSOMAL GEL

From the above tables no( ), it was verified the ethosomal gel release theory of GF4, GF5, GF6, GF7, GF8, GF9 up to 24 hours in products. And it was also confirmed from the table that the formulation (GF6) showed maximum drug release of up to 24 hours in both products.

PHARMACOKINETIC PROFILES FOR GF6 ETHOSOMAL GEL

Table 15: Release kinetics for optimized formulation.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	2.957925303	-0.05439445	17.25120161	0.38390172
Intercept	37.11954601	1.806980214	24.37709307	1.58555375
R 2	0.611771069	0.949144503	0.842450504	0.82013441

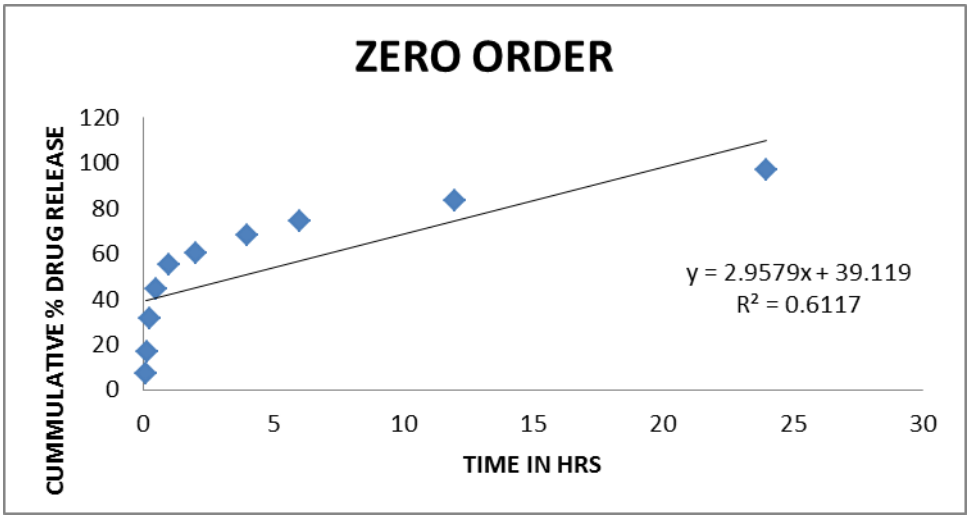

Figure 13: Zero Order Kinetics ForGF6Ethosomalgel.

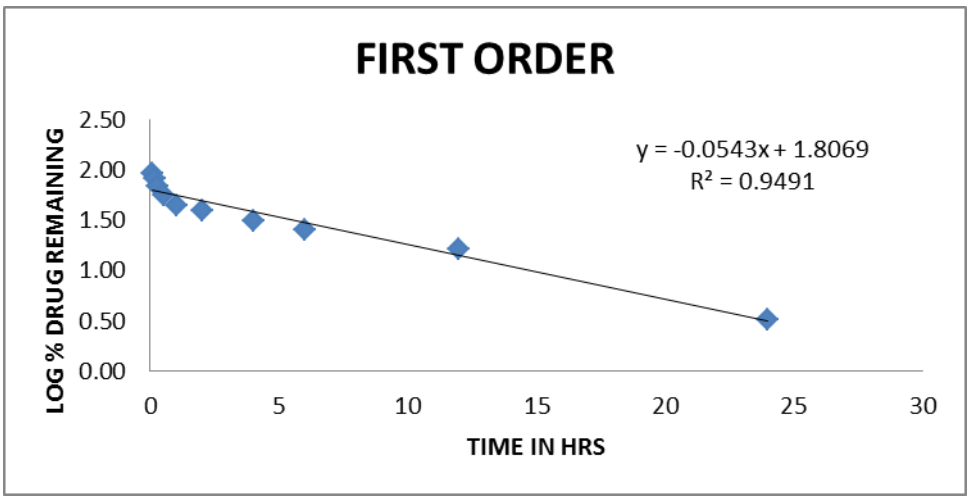

Figure14: First Order Kinetics For GF6Ethosomalgel.

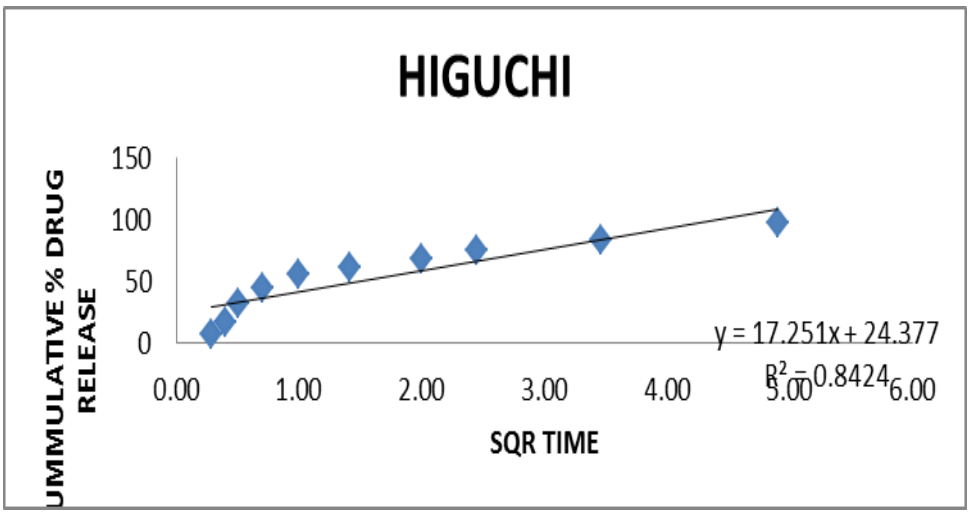

Figure 15: Higuchis model For GF6Ethosomalgel.

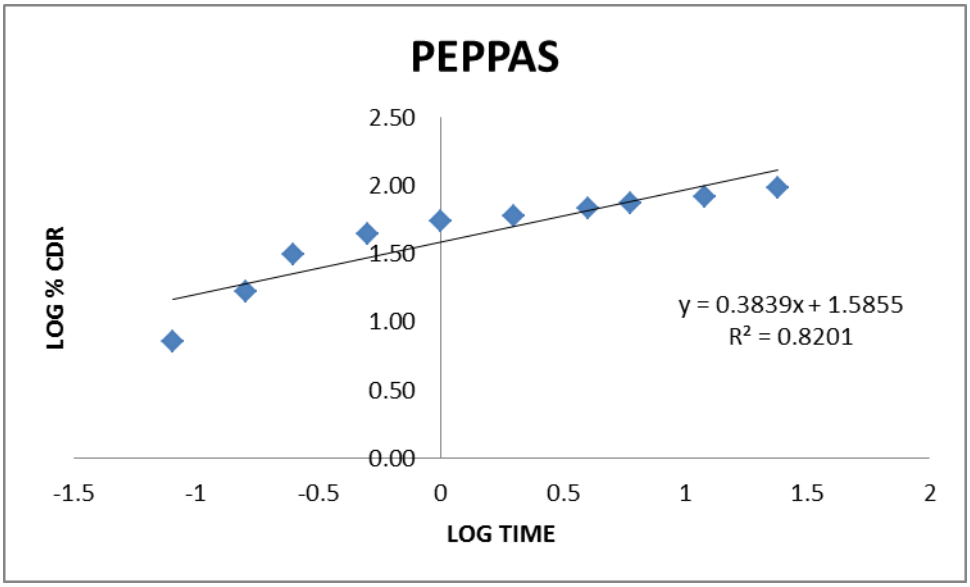

Figure 16: Peppas model For GF6 Ethosomal gel.

Stability studies

The stability experiments were performed in conjunction with the protocol mentioned in the section of the chapter. The findings are seen in the table below.

Table 16: % Entrapment efficiency and % Drug content after stability studies.

Number of Days	% Entrapment Efficiency at temperatures			% Drug Content at temperatures		
	4±2°C	25±2°C	37±2°C	4±2°C	25±2°C	37±2°C
15	84.8	84.8	84.8	98.6	98.47	98.60
30	84.79	84.48	83.49	98.12	98.92	98.71
45	84.26	83.28	83.27	97.11	98.42	98.50
90	83.47	83.22	82.78	97.42	98.34	98.02

Table 17: Cumulative in-vitro percent drug release profile for Glibenclamide Ethosomes Optimized GF6 formulation at various temperatures.

S.No	Time in hrs	4±2°C	25±2°C	37±2°C
1	**0**	0	0	0
2	0.08	5.942	6.4476	6.134
3	0.16	15.1530	16.428	15.630
4	0.25	28.7	30.91	29.42
5	0.5	39.59	42.930	40.845
6	1	50.634	54.897	52.236
7	2	54.815	59.431	56.546
8	4	61.18	66.332	63.112
9	6	67.07	72.718	69.188
10	12	78.47	85.078	80.948
11	24	89.015	96.511	91.826

"S.No	Diffusion	Exponent (n) Overall solute Diffusion mechanism
1.	0.45	Fickian diffusion
2.	0.45<n<0.89	Anomalous (non-Fickian) diffusion
3.	0.89	Case-II transport
4.	n>0.89	Super case-II transport"[19]

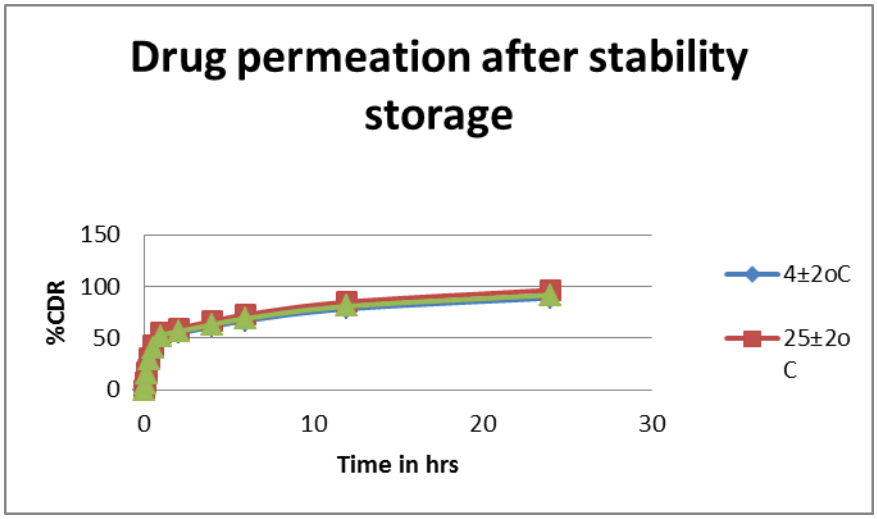

Figure 17: Graph showing dissolution profile for formulations GF6 after storage at different temperatures.

SUMMARY

There are some possible benefits of the Transdermal path over traditional routes. These benefits include the prevention of first-pass digestion, the predictable and sustained duration of action, the minimization of adverse side effects, the effectiveness of short half-life medications, the enhancement of physiological and pharmacological reactions, and, most notably, the avoidance of changes in blood levels. It offers comfort for patients. Yet poor penetration rates are one of the big issues with successful drug delivery.

The vesicular mechanism (liposomes and niosomes) is emerging as the next step in enhancing the topical delivery of drugs. Liposome technology has improved, so much so that they can now be called "Ethosomes", along with the "system" which has greater transdermal flux as it produces little skin inflammation and produces excellent skin depositing capability. With little change, the mixture of Glibenclamide ethosomes was prepared using the method stated by Touitou *et al*., (2000). Ethosomes containing 20 percent, 30 percent, & 40 percent IPA with sonication were tested.

After verifying the presence of vesicles and their duration, ultra centrifugation was tested for drugs trapped by the vesicular system. Sonicated ethosomes showed higher value i.e. 96.7 percent containing 40 percent w/w IPA. The dialysis membrane was used to conduct in-vitro liberation. The first order was found to be the order of drug release for optimised gel formulation. The ethosomes containing 30 percent w/w IPAA have considered the percentage of opioid concentration in the skin to be maximum.

CONCLUSION

In the present work, the mixture of ethosomal gels glibenclamide has been photmulated.

- The findings of this research suggest that the process of ion gelation can be successfully used to generate ethosomal gels of glibenclamide.
- The physical mixture's FT-IR spectrum showed that the drug is consistent with the polymers and copolymers used.
- Carbopol and IPA comprising ethosomal gels and phospholipids had a minimum size length of 613µm.
- Increased polymer concentration contributed to an improvement in the efficacy of drug entrapment, particle size, percentage.
- As the polymer and copolymer concentration increased, the in vitro drug release decreased.
- In comparison with other formulations, GF6 displays maximal drug release in 1440 min, across all formulations.
- Drug release mechanism review found that the drug release from the formulations followed the mechanism of non-fickian diffusion and followed first-order kinetics.
- Based on the results of evaluation tests, GF6 coded formulation was considered to be the best formulation.

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