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Formulation and Evaluation of Betamethasone Dipropionate EthosomalGel

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ABSTRACT: Ethosomal gel which is glucocorticoids with anti-inflammatory and immunosuppressive abilities. The main objective of the study is to develop and evaluate transdermal delivery system that is being well absorbed topically and has improved bio availability. Transdermal delivery system delivers drug in pre-determined and controlled rate that makes use of human skin as a port of eThe Aim of the present study is to formulate and evaluate Betamethasone Dipropionate ntry for systemic delivery of drug molecules. Liposomes are of little or no value as carrier of drug molecules because they don't penetrate into the skin so the ethosomal delivery system is preffered. Ethosomes which is an ethanolic liposome's that are noninvasive delivery carriers that enables drug to reach deep into the skin layers. Pre-formulations studies like organoleptic properties, solubility studies, melting point and FTIR for physical mixtures have been performed. They are prepared by cold method by means of sonication. Ethosomal vesicles are incorporated into corbopol gel and triethanolamine to make an ethosomal gel. Physicochemical characteristics like surface morphology, optical microscopy, entrapment efficiency(82.2%), In-vitro release study (drug release of 87.55%) have been performed and finally the drugs are also been evaluated by suitable methods like washability, viscosity, PH determination, drug content uniformity(95.62% of BD ethosomal gel). Thus, Transdermal delivery system has long duration of action of drug and avoidance of first pass metabolism and the gel is been made use for its anti- inflammatory action.

Keywords: Transdermal deliverysystem, Ethosomal gel, cold method, Anti-inflammatory action.

I. INTRODUCTION

Innovations within the area of drug delivery are happening at a way faster pace ascompared with the last 20 years . Improved patient compliance and effectiveness are inextricable aspects of latest drug delivery systems. A more radical approach has been to explore newer interfaces on the body for introducing therapeutics. One such approach, transdermal drug delivery, makes use of human skin as a port of entry for systemic delivery of drug molecules. Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devices of defined area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to succeed in the circulation . Transdermal delivery provides a number one edge over injectables and oral routes by increasing patient compliance and avoiding first-pass metabolism, respectively. Transdermal route has vied with oral treatment because the most successful innovative research area in drug delivery, as oral treatment involves attainment and maintenance of drug concentration within the body within a therapeutically effective range by introduction of a hard and fast dose at regular intervals, thanks to which the drug concentration within the body follows a peak and trough profile, leading to a greater chance of adverse effects or therapeutic failure; great deal of drug is lost within the vicinity of the organ and shut attention is required to monitor therapy to avoid overdosing.

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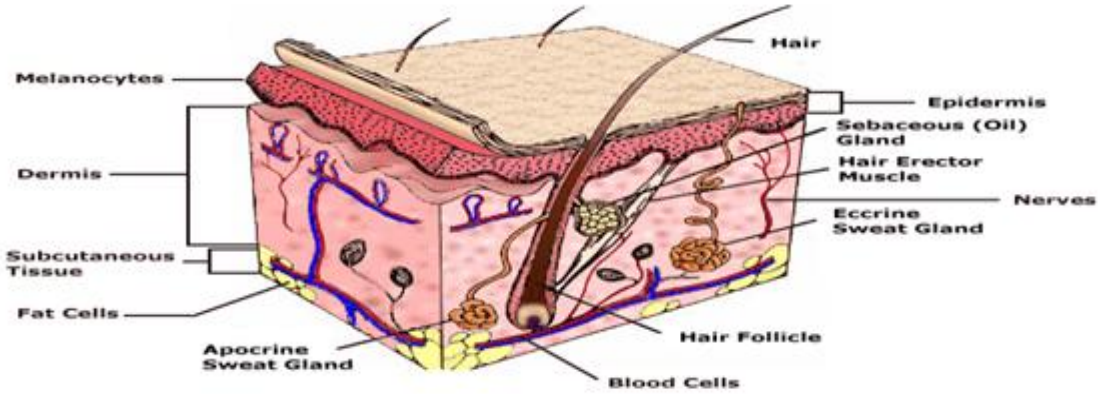

Figure : 1 STRUCTURE OF SKIN

ETHOSOMES

"Ethosomes are ethanolic liposomes". Ethosomes are often defined as noninvasive delivery carriers that enable drugs to succeed in deep into the skin layers and/or the circulation . These are soft, malleable vesicles tailored for enhanced delivery of active agents.

The vesicles are documented for his or her importance in cellular communication and particle transportation for several years. Vesicles would also allow controlling the discharge rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and thus be able to release just the proper amount of drug and keep that concentration constant for extended periods of your time . One of the most advances in vesicle research wasthe finding of a vesicle derivative, mentioned to an Ethosomes.

Ethosomes are the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. Ethosomes are soft vesicles made from phospholipids and ethanol (in higher quantity) and water.

The size range of Ethosomes may vary from tens of nanometers (nm) to microns (μ) Ethosomes permeate through the skin layers sooner and possess significantly higher transdermal flux.

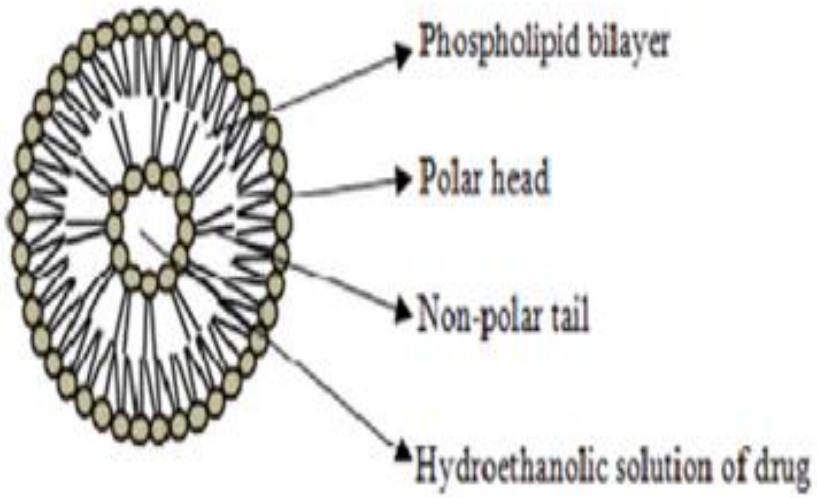

Figure : 2 STRUTURE OF ETHOSOME

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MATERIALS

Materials	Source
Betamethasone dipropionate	Central drugs & pharmaceuticals ,Chennai
Phospholipids (soya lecithin)	Hi media, Mumbai
Ethanol	Central drugs & pharmaceuticals ,Chennai
Propylene glycol	Robert Johnson
Cholesterol	SD fine chemicals, Mumbai
Carbopol 934 powder	Dr. Milton laboratories, Chennai
Triethanolamine	Robert Johnson

Table No : 1 List of Materials used

II. EXPERIMENTAL METHODS

PREFORMULATION STUDIES

Preformulation testing is the first step in rational development of dosage forms of a drug substance. Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies were performed for the obtained sample for identification and compatibility studies.

ORGANOLEPTIC PROPERTIES

The general appearance like nature, color, odor, etc. were performed by visual observations and compared with standard of drug given in pharmacopoeia for identification of drug.

Color: Small quantity of drug were taken on butter paper and viewed in well illuminated place.

Odor: Very less quantity of drug were smelled to get the odor.

SOLUBILITY STUDY

To know the solubility of Betamethasone dipropionate solubility study is performed in water, ethanol, methanol, phosphate buffer pH 7.4 and propylene glycol.

SOLUBILITY IN WATER

Known amount of Betamethasone dipropionate is dissolved in 5ml of distilled water andthesolutionisfilteredbyusingwhatmannfilterpaper.Theabsorbanceoffiltrateis measured spectrophotometrically by using distilled water asblank.

SOLUBILITY IN ETHANOL

Known amount of Betamethasone dipropionate is dissolved in 5ml of ethanol and the solution is filtered by using whatmann filter paper. The absorbance of filtrate is measured spectrophotometrically by using ethanol as blank.

SOLUBILITY IN METHANOL

Known amount of Betamethasone dipropionate is dissolved in 5ml of methanol and the solution is filtered by using whatmann filter paper. The absorbance of filtrate is measured spectrophotometrically by using methanol as blank.

SOLUBILITY IN PHOSPHATE BUFFER pH 7.4

Known amount of BD is dissolved in 10ml of phosphate buffer pH 7.4 and the solution is filtered by using whatmann filter paper. The absorbance of filtrate is measured spectrophotometrically at 239nm.

SOLUBILITY IN PROPYLENE GLYCOL

Known amount of Betamethasone dipropionate is dissolved in 5 ml of propylene glycol and the solution is filtered by using whatmann filter paper. The absorbance of filtrate is measured spectrophotometrically by using propylene glycol as blank.

MELTING POINT

For determination of freezing point USP

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method was followed. Small quantity of drug were placed into a sealed capillary tube. The tube was placed in the melting point apparatus. The temperature within the apparatus was gradually increased and therefore the refore the observation of temperature was noted at which drug began to melt and the temperature when the whole drug gets melted was noted.

COMPATIBILITY STUDIES

Fourier Transform Infra Red Spectroscopy studies:
The Fourier Transform Infra Red analysis were conducted for the structure characterization.

REAGENT PREPARATION

Preparation of standard drug solution

An accurately weighed quantity of 100 mg of Betamethasone dipropionate were taken in the 100 ml capacity volumetric flask and 100ml of phosphate buffer pH7.4 were added. This is labeled as stock solution. It contains 1mg/ml of drug.

Preparation of standard graph of BD

From the stock solution 10 ml were taken in a 100ml of volumetric flask and the solution were made up to 100ml with ethanolic phosphate buffer pH7.4. This solution containing 100µg/ml. From that series of dilution containing 10, 20, 30,40 and 50µg/ml of BD solution. The absorbance of the above dilution were measured in UV spectrophotometer at 239 nm using the buffer of pH 7.4 buffer solution as blank. The concentration of BD and corresponding absorbance as given in the below table. The absorbance were plotted againstconcentration of BD and this calibration curve were used for estimating the BD in the samples.

PREPARATION OF ETHOSOMES

COLD METHOD

- Ethosomal formulations were prepared by using the cold method.
- The ethanolic vesicular system composed of phospholipids (20% to 40%w/v), ethanol (20% to 40% v/v), propylene glycol (20 % v/v), drug and distilled water.
- Phospholipids were dissolved along with the drug in ethanol. This mixture was heated to 400C and a fine stream of distilled water was added slowly, with constant mixing at 700rpm with a mechanical stirrer in a closed container.
- Mixing were continued for an additional 5min, while maintaining the system at 400C.
- The preparation were left to cool at room temperature for 30min and then it were sonicated at 400C for five cycles of 3min each with a minute rest between cycles using probe solicitor.
- Eight formulation were prepared using different concentration of phospholipid and ethanol among them optimized formulation were selected for characterization and evaluation studies.

CLASS	EXAMPLE	USES
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Alcohol	Ethanol Isopropyl alcohol	For providingthesoftnessfor vesicle membrane
Polyglycol	Propylene glycol Transcutol alcohol	As a skin penetration enhancer
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123 Rhodamine red Fluorescene isothiocynate(FITC)	For characterization study

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Table No: 2 DIFFERENT ADDITIVES EMPLOYED IN FORMULATION OF ETHOSOMES

PREPARATION OF ETHOSOMAL GEL

- Best achieved Ethosomal vesicles suspension were incorporated into The carbopol gel (1%, 1.5%, 2%, W/W).
- The specified amount of carbopol 934 powders is to be slowly added to ultrapure water and kept at 100℃ for 20min.
- Triethanolamine were added to it dropwise. Appropriate amount of 1.5% w/w formulation containing drug were incorporated into gel base.
- Water q.s were added with other formulation ingredients should be achieved.
- Gel containing free drug were prepared by similar method using 1.5% Carbopol.

Gel formulation	**Betamethasone dipropionate Ethosomal suspension (ml)**	**Carbopol (%)**	**Triethanolamine (ml)**	**Buffer (pH 7.4)**
G1	20	1	0.5	q.s
G2	20	1.5	0.5	q.s
G3	20	2	0.5	q.s

Table No : 3 COMPOSITION OF BETAMETHASONE DIPROPIONATE ETHOSOMAL GEL

S. NO	**Ethosomal Formulation**	**Betamethasone dipropionate (g)**	**Phospholipids (soya lecithin) (%)**	**Cholesterol (g)**	**Propylene** glycol	**Ethanol (%)**
1	F1	0.20	2	0.005	10	20
2	F2	0.20	3	0.005	10	20
3	F3	0.20	4	0.005	10	20
4	F4	0.20	5	0.005	10	20
5	F5	0.20	2	0.005	10	30
6	F6	0.20	2	0.005	10	40
7	F7	0.20	3	0.005	10	30
8	F8	0.20	3	0.005	10	40

Table No: 4 COMPOSITION OF DIFFERENT ETHOSOMAL FORMULATION OF BETAMETHASONE DIPROPIONATE

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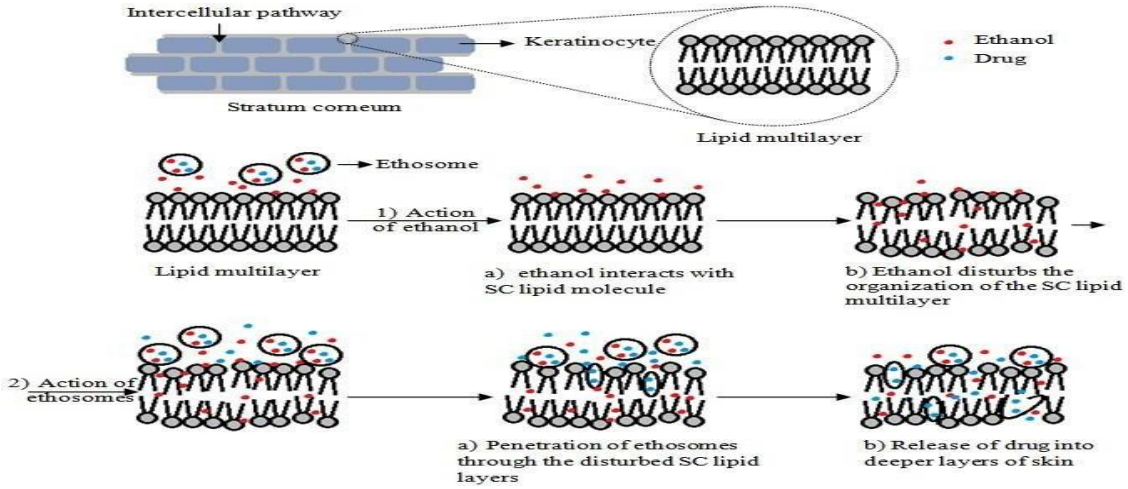

Figure No: 3 PROPOSED MECHANISM FOR DELIVERY OF ETHOSOMAL SYSTEM

EVALUATION TEST FOR ETHOSOMAL GEL

WASHABILITY

VISCOSITY

Viscosity was determined by Brookfield viscometer, spindle S64 and the angular velocity was found to be increased from 5,10,50,100 rpm and the values were noted.

SPREADABILITY

Spreadability of gel were determined by modified wooden block and glass slide apparatus. A measured amount of gel should be placed on fixed glass slide; the movable pan with a glass slide attached to it and can be placed over the fixed glass slide, such that the gel were sandwiched between the two glass slides for 5min. The weight can be continuously removed. Spreadability were determined using the formula.

S = ML/T

Where,

S- is the Spreadability in g/s

L- Is the length of glass slide

M- Mass in grams

T-is the Time in seconds

pH MEASUREMENT

1gm Betamethasone dipropionate Ethosomal gel were mixed in 100ml distilled water with homogenizer. Then the electrode were immersed in prepared gel solution and readings were recorded from digital pH meter in triplicate and average value were calculated.

DRUG CONTENT UNIFORMITY

A measured amount of formulated gel were taken and dissolved in 100ml of buffer pH7.4. Mechanical shaker were used to shake the gel solution continuously for 2hrs. The solution thus prepared were to be filtered and analyzed spectrophotometrically at 239nm using suitable phosphate buffer (pH 7.4) as blank.

***INVITRO*RELEASE STUDIES**

ETHOSOMAL GEL

The BD Ethosomal gel were studied using a modified Keshary-chein diffusion cell. A standard cellophane membrane (soaked in pH 7.4 for 2hrs before use) were fixed to a minimum of one end of the cylinder with the assistance of an adhesive end in the permeation cell. 1gm was taken in the cell (donor compartment) and the cell were immersed in beaker (100ml) containing drug free phosphate buffer pH7.4 (90ml) as a receptor compartment.

The cell was immersed to a depth of 1cm below the surface of phosphate buffer in the receptor compartment and agitated using a magnetic stirrer and a temperature of 320c ± 10c was maintained.

Sample (5ml) of the receptor compartment was taken at various intervals of time over a period of4hrs and assayed under the absorbance at 239nm.

The Volume withdrawn at whenever was replaced with Drug free phosphate buffer . Amount of BD released at various intervals of Time were calculated and plotted against Time.

HOMOGENICITY

A small quantity of Ethosomal gel were

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pressed between the thumb and the index finger. The consistency of the Ethosomal gel were noticed (whether homogenous or not), if there were any coarse particles appeared on fingers. Also, the homogeneity might be detected when a little quantity of the Ethosomal gel were rubbed on the skin of the rear of the hand.

STABILITY STUDIES

The stability studies for optimized formulation should be conducted in the accelerated conditions as per guidelines of International Conference on Harmonization (ICH). Well closed container were used for the storage of optimized gel formulation. The gel formulations will be stored at 40˚C and 75% relative humidity for 90 days.

Samples were drawn at a forethought time interval of 30 days, 60 days and 90 days. The gel formulation can be evaluated for their physical properties including appearance, color, and presence of clogs, consistency and phase separation. Gel can also be evaluated for chemical parameters like change in pH and drug content.

III. RESULTS AND DISCUSSION

EVALUATION TESTS

ORGANOLEPTIC PROPERTIES

Prue BD was examined for color, odor and appearance

Drug	Test	Specification	Observation
Betamethasone dipropionate	Color	White crystalline powder	White powder
Betamethasone dipropionate	Odour	Odourless	Odourless
Betamethasone dipropionate	Appearance	Fine crystalline powder	White powder

Table no : 5 ORGANOLEPTIC PROPERTIES OF BD

The observations noted were compared to the specifications given in the pharmacopoeia to confirm the identity of the drug and it were found that observations noted complied with the specifications.

SOLUBILITY STUDY

Solubility studies are performed to determine the solubility of drug in different solvent.

S.NO.	Quantity of drug	Solvent	Quantity of solvent	Inference
1.	50 mg	Distilled Water	5 ml	Insoluble
2.	50 mg	Ethanol	5 ml	Soluble
3.	50 mg	Methanol	5 ml	Sparingly soluble
4.	50 mg	Phosphate buffer pH 7.4	5 ml	Very Sparingly soluble

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6.	50 mg	Propylene glycol	5 ml	slightly soluble

Table no: 6 Solubility of Betamethasone dipropionate in various solvents.

MELTING POINT

Melting point of Betamethasone dipropionate were found to be 1770C. Melting point were measured three times and mean were noted. A sharp transition took place from solid to liquid at 177℃, indicating that the sample were pure and free from impurities.

COMPATIBILITY STUDIES BY FTIR

FIGURE : 4 FTIR PROFILE OF PURE BETAMETHASONE DIPROPIONATE

S.No	VIBRATIONS	RANGE
1	OH Stretching	3475
2	C=OStretching	1658
3	C-CStretching	2931
4	C=CStretching	1616

Table no : 7 FTIR SPECTRA INTERPRETATION OF BD

ENTRAPMENT EFFICIENCY

Formulation code	Entrapment efficiency (%)
F1	88.2
F2	79.5
F3	83.5
F4	82.3
F5	79.2
F6	69
F7	73.4
F8	75.7

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***INVITRO* STUDIES**

Table no : 9*INVITRO* DRUG RELEASE PROFILE OF BETAMETHASONEDIPROPIONATE ETHOSOMAL FORMULATION (F1-F4)

Time (hr)	F1	F2	F3	F4
0	0	0	0	0
1	14.3	9.8	8.9	13.0
2	16.9	12.9	11.4	15.9
3	23.4	17.6	15.1	20.4
4	27.6	20.0	18.4	24.7
5	37.3	29.5	25.8	34.7
6	42.5	32.3	28.6	41.4
7	51.9	38.2	34.7	49.6
8	64.8	46.2	41.5	61.2

Time (hr)	F5	F6	F7	F8
0	0	0	0	0
1	6.9	7.8	10.5	7.6
2	12.6	12.2	21.3	17.8
3	17.0	15.4	28.8	24.2
4	22.3	17.6	33.4	29.0
5	25.4	19.9	38.9	34.3
6	28.1	22.8	43.9	39.9
7	32.2	28.4	55.8	47.8
8	39.6	35.3	67.8	57.6

Table no: 10 *INVITRO* DRUG RELEASE PROFILE OF BETAMETHASONE DIPROPIONATE ETHOSOMAL FORMULATION (F5-F8)

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EVALUATION OF ETHOSOMAL TOPICAL GEL

WASHABILITY

They are easily washable without leaving any residue on the surface of the skin.

VISCOSITY

The viscosity of the BD Ethosomal gel was found to be 36418 cps at 100rpm shear rate.

SPREADABILITY

The spreadability of BD Ethosomal gel was considered high by having a low spread of time. The therapeutic efficacy of gels depends on their spreading capacity. The gel spreading helps within the uniform application of the gel to the skin, so the prepared gels must have a acceptable Spreadability and satisfy the suitable quality in topical application.Spreadability was within the range of 8.4 to 15gm.cm/sec.

pH DETERMINATION

The pH were measured three times and mean were noted. Hence pH of Betamethasone dipropionate were found to be 6.2.

DRUG CONTENT UNIFORMITY

S.NO	FORMULATIONCODE	DRUG CONTENT (%)
1	EG1	95.62
2	EG2	90.51
3	EG3	89.62

Table no :11 DRUG CONTENT OF ETHOSOMAL GEL

*INVITRO*RELEASE STUDIES OF BETAMETHASONE DIPROPIONATE ETHOSOMAL GEL

Time (hr)	EG1	EG2	EG3
0	0	0	0
1	13.65	19.68	22.9
2	25.72	28.48	30.01
3	42.36	33.02	35.6
4	49.82	42.6	47.1
5	56.86	49.7	53.5
6	63.59	54.77	62.22
7	78.09	60.1	70.6
8	85.77	68.44	75.5

Table no : 12 *Invitro* drug release profile for Betamethasone dipropionate Ethosomal gel(EG1-EG3)

HOMOGENICITY

The developed Ethosomal gel formulations was characterized for homogeneity assessment. This was done by inspecting visually the gel after the settlement of gel in suitable containers. Gel which exist good in nature.

STABILITY STUDIES

The stability studies were performed at 400C±20C/75%RH as per ICH guidelines. Samples were analyzed at periodic time intervals for 3 months for the estimation of pH and drug content. It were observed that there were no change in the physical appearance of the formulation.

The drug content were analyzed and there were a marginal difference between the formulations stored at different temperatures as shown in table.

Ethosomal topical gel formulations retained good

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stability throughout the study.

PARAMETERS	INITIAL	1 MONTH	2 MONTHS	3MONTHS
pH value	6.9	7.0	7.0	7.0
Drug content	95.67	94.3	92.1	91.03
Viscosity at 100rpm	36418	36417.6	36019.7	3598.9

Table no ; 13 STABILITY STUDIES OF BD ETHOSOMAL GEL

IV. DISCUSSION

- In-vitro release for Ethosomal formulation was carried out using dialysis membrane showed higher value i.e. 67.8% of 7th hour.
- In order to investigate the possible interaction between the drug and selected polymers, FTIR spectroscopy studies were carried out. IR spectrum of pure drug and physical mixture of drug-polymers were obtained and characterized.
- It was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which shows there were no physical interaction because of some band formation between drug and polymers.
- Various evaluation test also carried out with BD Ethosomal gel involving Washability, spreadability, pH determination, drug content uniformity, In Vitro studies, homogeneity and stability studies.
- The gel spreading helps in the uniform application of the gel to the skin, so the prepared gel have good spreadability and satisfy the ideal quality in topical application.
- Drug content uniformity were estimated and showed higher value i.e., 95.62% of BD ethosomal gel.
- *In-Vitro* release studies also performed for BD ethosomal gel and observed highest drug release of 85.77%.
- The stability studies were carried at for 3month as per ICH guidelines. It was observed there were no change in the physical appearance of the formulation.

V. SUMMARY AND CONCLUSION

It is documented that if drug molecules presenting any difficulties in its solubility and bioavailability along the alimentary canal are candidates for other routes of administration and if the site of action for drug candidate is subdermal, most effective penetration enhancers are needed to transport the drug molecule deeper into skin tissue for optimized therapeutic delivery of drug.

It is generally agreed that classic liposomes are of little or no value as carriers for transdermal drug delivery because they are doing not penetrate the skin. Recently derived ethosomal system can deliver drug molecules into and thru the skin. An attempt was made to prepare the highly efficient ethosomal drug delivery system using Itraconazole as model drug.

The techniques used were simple and reproducible. The formulated ethosomes were spherical and discrete in shape. However, ethosomes formulated by sonication method were more uniform and smaller in size which is important for skin penetration.

While comparing the efficiency for Entrapment , ethosomes containing 30% w/w ethanol and ready by sonication showed highest value reference to all other formulation. So it's concluded ethosomal prepared by sonication and containing 30

% w/w ethanol because the best formulation considering all other aspects. The highest value of transdermal flux for sonicated ethosomes containing 30% w/w ethanol is that the indication of complete and rapid penetration through the

skin could also be due to tiny vesicular size.

This is an encouraging observation for drugs which are poorly absorbed from skin When effect of sonication was compared on ethosomal formulation, sonicated formulation possessed better or suitable characteristics (smaller size, uniform size, distribution, highest entrapment efficiency).

From the above observations it are often concluded sonication is an important tool for the preparation of ethosomes. Thus, the specific objectives listed in the introduction were achieved namely design, characterization and release studies of Itraconazole ethosomes.

Certainly these finding can be applied for transdermal drug delivery of Betamethasone dipropionate for treatment of skin irritation, rashes.

The present study has been concluded that Ethosomes has an advantages of rapid onset and maximum release of drug with reduction of side effects. These findings may help the industry for development and scaling up a replacement formulation.

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