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FORMULATION AND EVALUATION OF TELMISARTAN LOADED ETHOSOMAL PATCH

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ABSTRACT

The aim of the present study was to develop telmisartan loaded ethosomal patch to improve bioavailability of telmisartan by avoiding the first pass metabolism. Ethosomes are lipid vesicular carriers containing ethanol which provides better penetration of drug in to skin. Telmisartan ethosomes were prepared by cold method (30°C), using different ratios of egg lecithin, cholesterol and ethanol. The formulated ethosomes were evaluated for all the physicochemical parameters such as particle size, zeta potential, SEM, entrapment efficiency and drug release. The best selected ethosomal formulationF11 showed an entrapment efficiency of 85% and drug release of 83.89% in 6hrs.The best selected ethosomal formulation of telmisartan was used to prepare ethosomal patch by using Hydroxy Propyl Methyl Cellulose (HPMC E15) as a film forming agent and dibutyl phthalate as a plasticizer. All the developed ethosomal patches of Telmisartan were evaluated for folding endurance, drug content, weight variation and *in-vitro* drug release. The *in-vitro* drug release was found to be 92.56% over a period of 24 hours. Based on the above results it can be concluded that administration of telmisartan ethosomes through transdermal route is a better approach.

KEYWORDS: Telmisartan, ethosomes, ethosomal patch.

INTRODUCTION

Targeting drugs by a carrier system has been a central theme of research in therapeutics. Several approaches have been investigated to deliver drugs via topical route. Targeting the drugs is usually attained by utilising a carrier such as albumin, conjugates, antibodies, lecithin's, glycoproteins, DNA, dextran, polysaccharides, ethosomes, nanoparticles and liposomes. The widespread interest in use of ethosomes as drug carrier requires the necessity of pharmaceutically acceptable procedure for the preparation and characterisation of ethosome vesicles. The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Researchers have been understanding the properties of vesicle structures for use in better drug delivery within their cavities, that would allow to tag the vesicle for cell specificity. Vesicles would also allow to control the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and would be able to release just the right amount of drug and keep that concentration constant for longer periods of time. One of the major advances in vesicle research was finding a vesicle derivative, known as an ethosomes. Ethosomes are ethanolic liposomes. Ethosomes can be defined as non-invasive delivery carriers that enable drugs to reach deep into the skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Vesicles would also allow controlling the release 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 right amount of drug and keep that concentration constant for longer period of time. One of the major advances in vesicle research was finding the vesicle derivative, known as ethosome. Ethosomal carriers are systems containing soft vesicles, ethanol at relatively high concentration and water. It was found that ethosomes penetrate through the skin and allow enhanced delivery of various compounds to the deep strata of the skin or to the systemic circulation.[1]

Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. The size of ethosomes can be modulated to any range from 30nm to few microns.

Ethosomes provide number of important benefits including improving the drug efficacy, enhancing patient compliance and comfort and reducing the total cost of treatment. Ethosomes are mainly used for the delivery of drugs through transdermal route. The transdermal delivery is one of the most significant routes of drug administration. The main factor which limits the application of transdermal route for drug delivery is the permeation of drugs through the skin. Human skin has selective permeability for drugs, only the lipophilic drugs having molecular weight<500 Dalton can pass through it. To overcome the stratum corneum barrier, various mechanisms have been investigated, including use of chemical or physical enhancers, such as sonophoresis, iontophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have the potential of overcoming the skin barrier and have been reported to enhance permeability of drug through the stratum corneum barrier. Ethosomes were designed to enhance the delivery of drugs into the deep layers of the skin and through the skin. Depending on the formulation, delivery can be targeted for local delivery or for systemic use. Ethosomal patch is a modified reservoir transdermal patch. Transdermal drug delivery systems (TDDS) allow delivery of a drug into the systemic circulation via permeation through skin layers at a controlled rate. Oral treatment involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of a fixed dose at regular dose due to which the drug concentration in the body follows a peak and trough profile, leading to a greater chance of adverse effects or therapeutic failures and large amount of drug is lost in the vicinity of target organ. Oral route requires close attention to monitor therapy to avoid over dosing. So transdermal drug delivery system appears to be most promising delivery system over conventional dosage forms in order to either avoid hepatic first-pass effect or to decrease the dosing frequency required for oral treatment.[2,3]

MATERIALS AND METHODS

Telmisartan was obtained as a gift sample from mylan laboratories, Hyderabad. Egg lecithin was obtained as a gift sample from Aurobindo laboratories, Hyderabad. Cholesterol, ethanol, propylene glycol and HPMC E15 were purchased from SD fine chemicals, Mumbai. All other chemicals used were of analytical grade.

Preparation of ethosomes using cold method

This is the most common method utilized for the preparation of ethosomal formulation. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol is added during stirring. This mixture is heated to 30˚C in a water bath. The water heated to 30˚C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. Finally, the formulation is stored under refrigeration.[4,5]

Table 1: Formulation of Ethosomes

Formulation code	Drug concentration(mg)	Lecithin (mg)	Cholesterol (mg)	Ethanol (ml)	Propylene glycol(ml)
F1	20	100	25	10	3
F2	20	200	25	10	3
F3	20	300	25	10	3
F4	20	400	25	10	3
F5	20	500	25	10	3
F6	20	400	35	10	3
F7	20	400	45	10	3
F8	20	400	55	10	3
F9	20	400	65	10	3
F10	20	400	75	10	3
F11	20	400	45	15	3
F12	20	400	45	20	3
F13	20	400	45	25	3
F14	20	400	45	30	3

EVALUATION OF ETHOSOMES

Determination of drug entrapment efficiency: Ethosomal formulations were centrifuged at 3000 RPM for 30 mins using ultracentrifuge to separate ethosomes from unentrapped drug. Concentration of the drug was determined by lysing the pellet using isopropyl alcohol and measuring absorbance at 296 nm using UV spectrophotometer. Percent drug entrapment was measured Dialysing the ethosomes with isopropanol after centrifugation and measuring absorbance at 296 nm.[6,7]

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug encapsulated}}{\text{Total amount of drug}} \times 100$$

***In-vitro* Diffusion studies**

In-vitro drug diffusion of ethosomal suspension was studied using a Franz diffusion cell. The semi permeable membrane is mounted between the donor and the

receptor compartment.

Ethosomal suspension is placed in donor compartment. The receptor compartment contained PBS maintained at 37 ˚C ±1 ˚C by magnetic stirrer. Samples were withdrawn through the sampling port of the diffusion cell at pre-determined intervals over 24 hours and analysed by UV - visible spectrophotometer at 296nm. An equal volume of fresh PBS was replaced into the receptor compartment after each sampling to maintain sink conditions.[8]

CHARACTERISATION OF ETHOSOMES

Surface morphological studies: SEM

The morphology of ethosomes was determined using scanning electron microscopy (Hitachi- S3700N). SEM gives a three-dimensional image of the globules. One drop of ethosomal suspension was mounted on a clear glass stub. It was then air then air dried and gold coated using sodium auro thiomalate to visualize under scanning electron microscope 10,000 magnification.[9]

Particle size measurement and zeta potential

The z-average diameter of sonicated vesicles was determined by dynamic light scattering using a particle size analyser (Horibo scientific nanopartica SZ 100). For measurement, 100µl of the formulation was diluted with an appropriate volume of PBS and the vesicle diameter and zeta potential were determined.[9]

Preparation of telmisartan ethosomal patch

- Dissolve weighed amount of HPMC E15 in solvent mixture of DCM and methanol (1:1) on a magnetic stirrer.
- 10 ml of ethosomal suspension containing 20mg drug was added to polymer solution during stirring to get uniform suspension of polymer solution
- After the formation of homogenous mixture dibutyl phthalate is incorporated as plasticizer and continuously mixed
- Obtained patches were stored in a desiccator to remove excess moisture. Solution is poured into moulds and dried for 24hrs at room temperature.[10]

Table 2: Formulation of ethosomal patch

Formulation	Drug concentration(mg)	HPMC E15 (mg)	DCM:M (1:1) (ml)	Dibutylpthalate (%)
ET1	20	300	6	15
ET2	20	400	6	15
ET3	20	500	6	15
ET4	20	600	6	15

EVALUATION OF ETHOSOMAL PATCH[11,12]

Thickness

Thickness of the patch can be measured using digital micro meter screw gauge at three different places, and the mean value was calculated.

Uniformity of weight

Patches are randomly collected and the weight is determined. The value reported must be the mean of three sets of experiments.

Folding Endurance

The folding endurance was measured manually for the prepared patches. It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. This was determined by repeatedly folding one patch at the same place till it breaks. The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance.

Drug content

A specified area of the patch is dissolved in a suitable solvent in specific volume. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically at wavelength of 296 nm and determined the drug content Initial weight.

In vitro drug diffusion study

The *in vitro* diffusion study is carried out using Franz Diffusion Cell. The semi permeable membrane is mounted between the donor and the receptor compartment. Ethosomal patch is placed in donor compartment. PBS is taken in the receptor compartment. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 37°C ± 0.5°C. Samples were withdrawn and replaced by equal volumes of fresh PBS on each occasion and analysed spectrophotometrically at 296nm.

RESULTS AND DISCUSSION

Entrapment efficiency: Entrapment efficiency was determined by lysing the ethosomal vesicles using isopropanol.

Table 3. (a): Entrapment Efficiency of the ethosomes prepared by varying the egg lecithin concentration.

S.no.	Formulation Code	%EE
1	F1	40.5±1.76
2	F2	48±1.72
3	F3	54.8±1.62
4	F4	78.6±1.51
5	F5	69.2±1.60

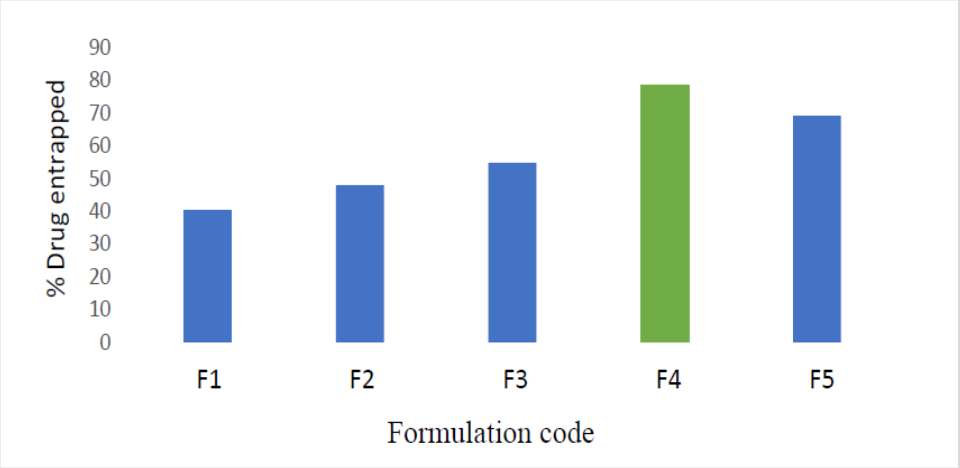

Fig 1: (a) Entrapment Efficiency of the ethosomes prepared by varying the egg lecithin concentration.

From the above table 3 (a) it was concluded that F4 was found to have the highest entrapment efficiency of 78.6%.

Table 3(b): Entrapment Efficiency of ethosomes prepared by varying the cholesterol concentration.

S. No.	Formulation Code	%EE
1	F6	78±1.72
2	F7	80.2±1.29
3	F8	67.5±0.77
4	F9	54.2±0.94
5	F10	40±1.51

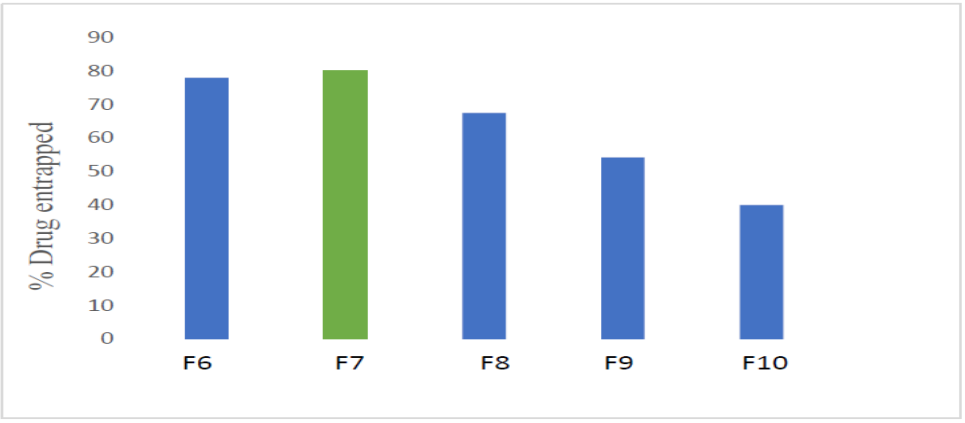

Fig 1 (b) Entrapment Efficiency of the ethosomes prepared by varying the cholesterol concentration.

From the above table 3 (b) it was concluded that F7 was found to have the highest entrapment efficiency of 80.2%. As the cholesterol concentration increased, entrapped efficiency was also found to be increased to some extent.

Table 3(c): Entrapment Efficiency of ethosomes prepared by varying the ethanol concentration.

S.NO.	Formulation Code	%EE
1	F11	85±0.84
2	F12	83.25±1.23
3	F13	81.56±1.02
4	F14	80.32±1.54

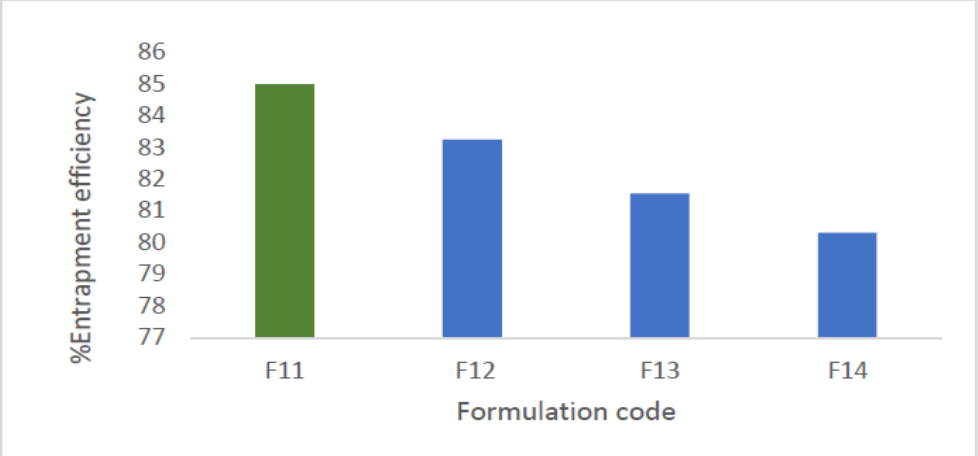

Fig 1: (c) Entrapment Efficiency of the ethosomes prepared by varying the ethanol concentration.

From the above table 3 (c) it was concluded that F11 was found to have the highest entrapment efficiency of 85%. As the ethanol concentration increased, entrapment efficiency was also found to be increased to some extent.

***IN VITRO* DRUG RELEASE**

The cumulative percentage of drug release profile in 6hrs from formulations F1-F5 were shown in table 4 (a)

Table 4(a): *in vitro* drug release of ethosomes prepared by varying the egg lecithin concentration.

Time(hr)	%DR of F1	%DR of F2	%DR of F3	%DR of F4	%DR of F5
0	0	0	0	0	0
1	17.5±0.98	18.2±1.56	18.9±1.23	20.8±0.52	19.6±1.52
2	28.64±1.5	29.98±1.47	30.8±1.72	33.6±0.89	25.78±1.29
3	40±1.09	41.45±0.96	42.96±1.27	45.26±1.32	39.8±1.39
4	51.9±0.73	53.08±1.75	54.99±1.76	59.5±1.03	50.67±1.87
5	60.03±0.81	61.95±1.93	63.09±1.59	67.23±1.53	64.95±1.40
6	69.34±1.87	70.56±1.42	72.8±1.03	78.39±1.02	73.96±1.21

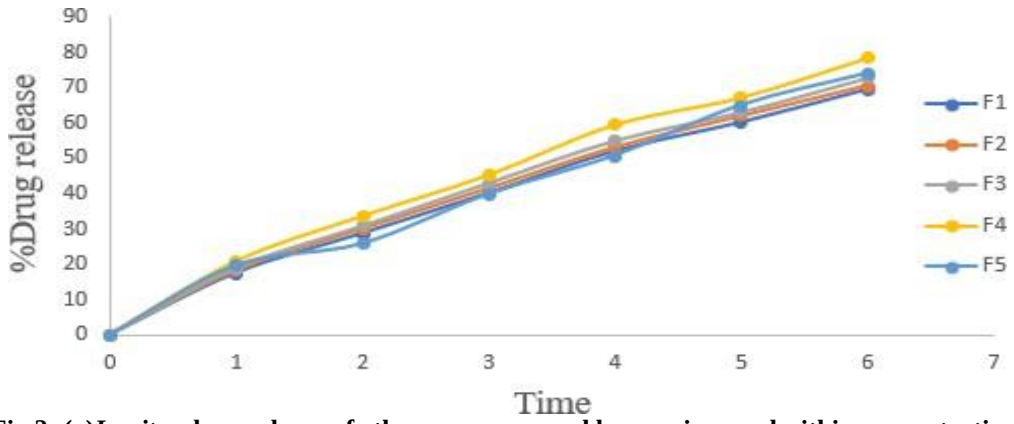

Fig 2: (a)*In-vitro* drug release of ethosomes prepared by varying egg lecithin concentration.

From the above fig 2 (a) it can be concluded that F4 formulation was found to have highest drug release of 78.39% at the end of 6th hour. It was observed that as the concentration of egg.

lecithin increased, drug release was increased to certain extent. Further increase in lecithin concentration resulted in decrease in drug release due to flocculation of excess lecithin.

The cumulative percentage of drug release profile in 6hrs from formulations F6-F10 were shown in table4 (b).

Table 4(b): *in vitro* drug release of ethosomes prepared by varying the cholesterol concentration.

Time(hr)	%DR of F6	%DR of F7	%DR of F8	%DR of F9	%DR of F10
0	0	0	0	0	0
1	18.34±1.05	26.83±0.92	25.76±0.97	23.2±1.07	21.09±1.39
2	23.53±1.23	38.67±1.42	32.63±1.34	30.19±1.82	29.97±1.42
3	35.14±1.52	50.4±1.28	48.85±1.07	44.34±1.27	38.75±1.09
4	49.38±2.90	62.72±1.93	60.07±1.49	53.67±1.40	50.96±1.34
5	57.9±1.54	74.89±1.45	71.45±1.38	65.49±1.67	61.76±1.84
6	68.78±0.92	81.43±1.03	78.23±1.73	69.82±1.02	64.98±1.06

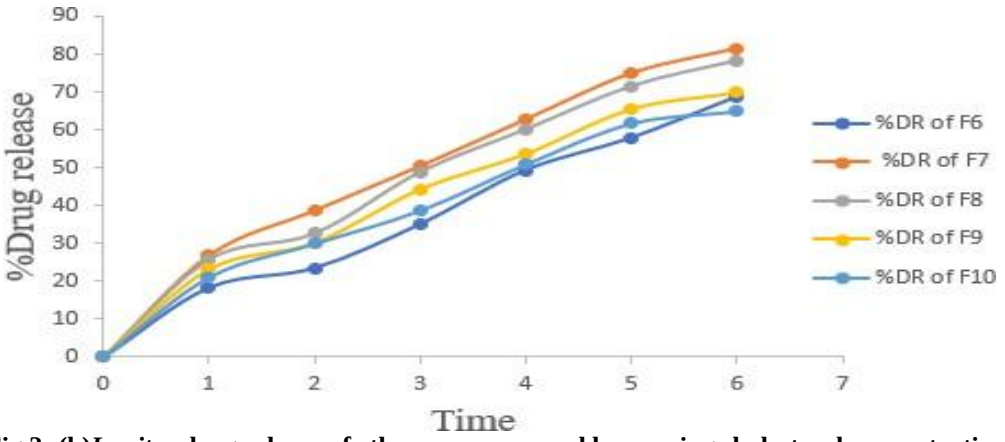

Fig 2: (b)*In-vitro* drug release of ethosomes prepared by varying cholesterol concentration.

From the above fig 2 (b) it can be concluded that F7 formulation was found to have highest drug release of 81.43% at the end of 6th hour. It was observed that as the concentration of cholesterol increased, drug release was increased to certain extent. Further increase in lecithin concentration resulted in decrease in drug release due to improper organisation of contents.

The cumulative percentage of drug release profile in 6 hrs from formulations F11-F14 were shown in table 4 (c).

Table 4(c): *in vitro* drug release of ethosomes prepared by varying the ethanol concentration.

Time(hr)	%DR of F11	%DR of F12	%DR of F13	%DR of F14
0	0	0	0	0
1	25.48±1.64	23.49±1.56	21.32±1.30	19.25±1.54
2	39.67±1.29	36.02±1.67	34.75±1.62	31.05±1.82
3	53.25±1.27	50.78±1.29	46.45±1.24	40.25±1.09
4	68.22±1.68	64.06±1.34	62.05±1.40	58.25±1.23
5	75.94±1.92	71.45±0.92	70.49±1.87	66.03±1.94
6	83.89±1.73	78.23±0.78	72.29±1.02	69.75±1.06

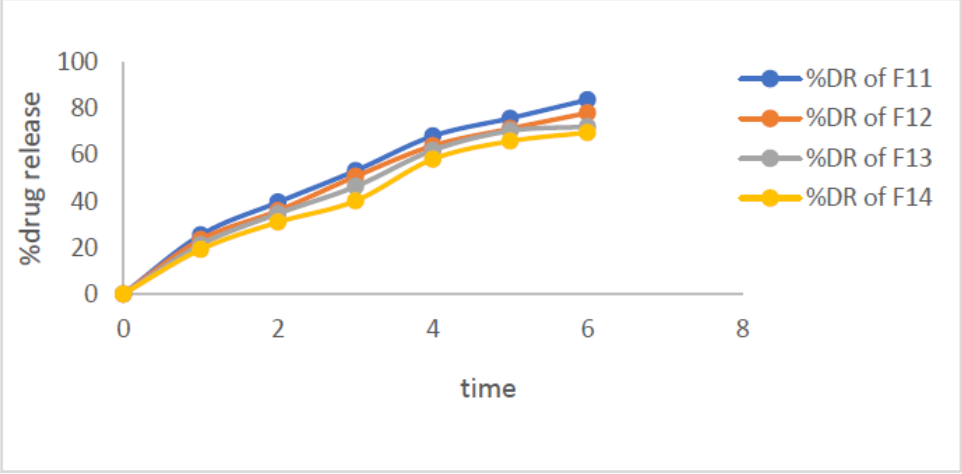

Fig 2: (c) *In-vitro* drug release of ethosomes prepared by varying ethanol concentration.

From the above fig 4.6 (c) it can be concluded that F11 formulation was found to have highest drug release of 83.89 % at the end of 6th hour. It was concluded that as the concentration of ethanol increased, drug release was increased to certain extent. Further increase in ethanol concentration resulted in decrease in drug release. This may be due to formation of thinner membrane.

CHARACTERIZATION OF ETHOSOMES

Ethosomes formulated with different ratios of cholesterol and egg lecithin ratios were evaluated for various physico-chemical parameters such as vesicle size and shape, zeta potential, polydispersity index, entrapment efficiency, release characteristics and stability studies.

Surface morphology

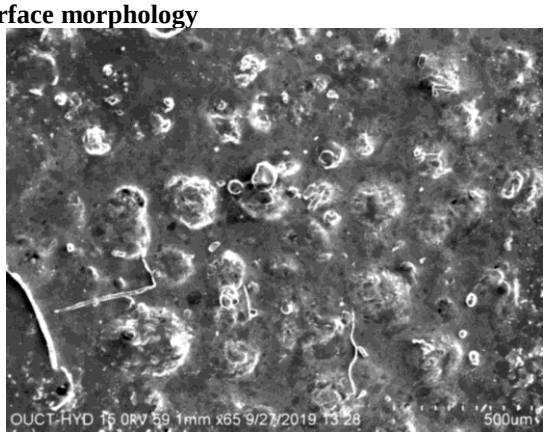

Fig 3(a). Scanning electron Microscopic Images of telmisartan Ethosomes.

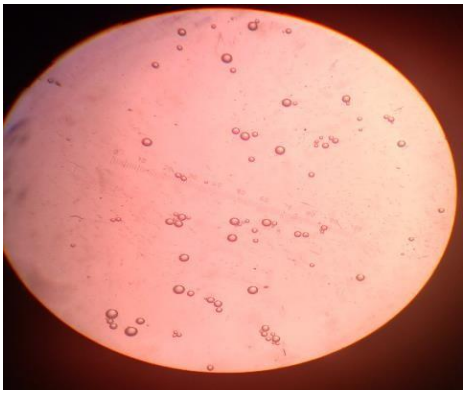

Fig.3(b): Photomicrograph of telmisartan Loaded Ethosomes.

From SEM images and microscopic evaluation, it was observed that most of the vesicles were smooth spherical in shape.

POLY DISPERSITY INDEX AND DROPLET SIZE

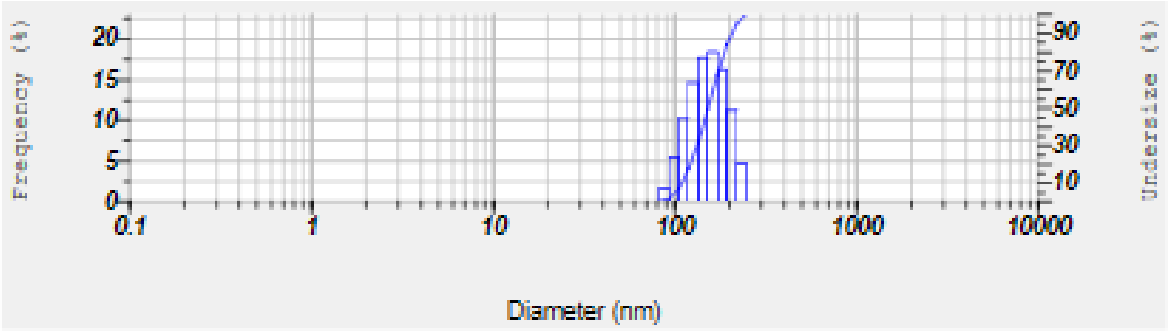

Fig. 4 Poly dispersity index and droplet size of ethosomes.

The ethosomal formulation had a poly dispersity index of 0.809 and average particle size was found to be 810.6 nm.

Zeta Potential

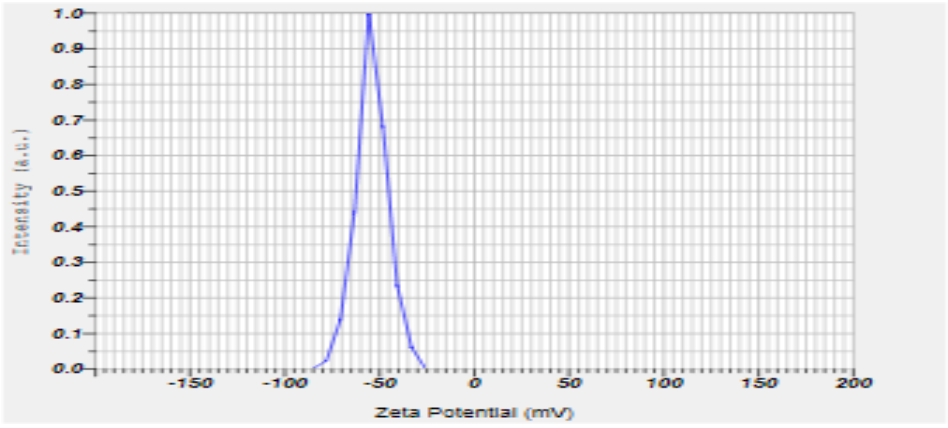

Fig. 5: Zeta potential of ethosomes.

The ethosomal formulation had a zeta potential value of -54.1 mV, which is a measure of net charge of the ethosomes. This higher charge on the surface of vesicles produced a repulsive force between the vesicles which made them stable and devoid of agglomeration and faster settling, providing an evenly distributed suspension. It can be concluded that the ethosomal formulations show good stability and hence were processed for formulation of patch.

STABILITY STUDIES

Stability studies were carried out for 2 months. During the study, none of the stored samples showed precipitation indicating that prepared formulations were physically stable under room and refrigeration storage conditions. Formulations stored at 40±5˚C showed precipitation. The drug content of niosomal suspensions under all storage conditions after 8 weeks is given in table 5.

Table 5: Stability conditions of formulated telmisartan ethosomes.

Parameter	Storage conditions	3 months
Drug content	28±3˚C	91.77%
	25±2˚C	94.32%
	45±2˚C	71.67%

The drug content in the formulation F11 did not show significant difference when stored at refrigeration and room temperatures. But the percentage drug content reduced when the formulations were stored at 45±2˚C. Hence, refrigeration and room temperature were considered as optimal temperature for storage of ethosomes.

EVALUATION OF ETHOSOMAL PATCH

Table 6: Physical characteristics of telmisartan ethosomal patch.

Formulation code	Weight variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)
ET1	144±1.26	0.16±0.05	150±1.56	82.5±0.016
ET2	142.6±1.25	0.14±0.02	158±1.85	83.89±0.02
ET3	141.9±0.99	0.19±0.02	155±1.02	85.36±0.05
ET4	142±2.3	0.18±0.02	153±1.25	85.1±0.03

The physico-chemical evaluation from table 6 indicates that the weight variation of the formulated patches varied between 141.9 to 144 mg. The thickness of the patches was in the range 0.14 to 0.19mm. Folding endurance was measured manually; it was between 150 to 158. The percentage drug content in all formulations varied between the range 82.5and 85.36%. This indicates that the drug dispersed uniformly throughout the polymeric film.

Table 7: In *vitro* drug release of ethosomal patch.

Time (hr)	%DR of ET1	%DR of ET2	%DR of ET3	%DR of ET4
0	0	0	0	0
1	20.34±1.89	23.83±1.45	25.76±1.28	23.2±1.26
2	29.53±1.35	31.67±1.28	32.63±1.62	30.19±1.65
3	40.67±1.78	47±1.09	48.85±1.89	44.34±1.28
4	54.69±0.67	51.72±1.76	60.07±1.98	53.67±1.83
5	60.35±0.95	64.89±1.38	71.45±1.23	65.49±1.12
6	72.65±1.28	74.61±1.7	76.96±1.07	70.5±1.49
7	78.36±1.75	77.12±1.26	80.69±1.72	76.55±1.19
8	84.36±1.72	85.22±1.44	87.51±1.15	82.94±1.58
24	88.02±1.62	89.64±1.01	92.56±1.32	88.11±1.29

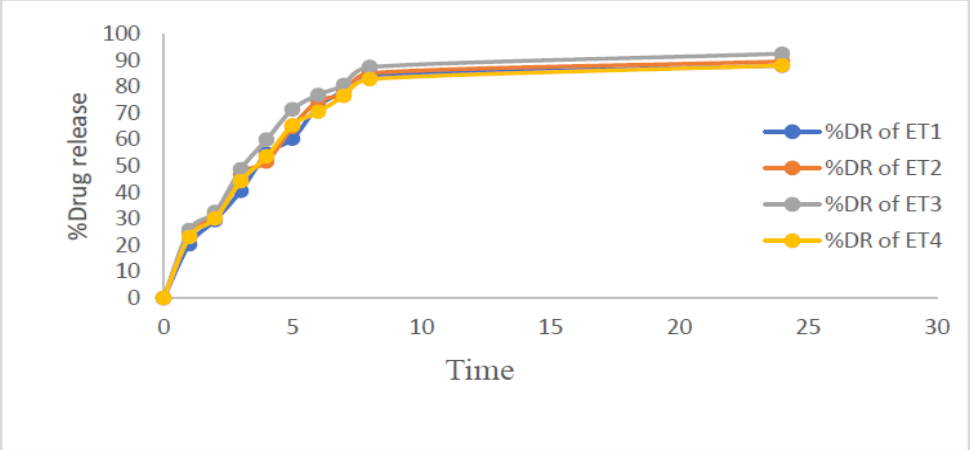

Fig 6: *In vitro* drug release of ethosomal patch.

From the above fig 6 it can be concluded that ET3 patch was found to have highest drug release of 92.56% at the end of 24th hour.

CONCLUSIONS

The incorporation of ethosomal systems in to a patch represents an important step to get better skin permeation and therapeutic results. Thus, ethosomes can become promising drug carrier in future for local and systemic disorders. The formulation was selected based on the entrapment efficiency and drug release studies. The formulation F11 was selected as best selected formulation from the twelve formulations. Since the entrapment efficiency and drug release was found to be 85 and 83.89% respectively. The best selected formulation F11 was formulated into patch. The best patch was selected based on characterisation such as drug content, weight variation, folding endurance and drug release. The patch ET3 was found to be best selected patch from the four patches, as the drug release was found to be 92.56%. The results revealed that formulation of ethosomal patch(micro-reservoir) prolonged the drug release of telmisartan in order to avoid frequency of dosing.

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