Formulation of mefenamic acid loaded transfersomal gel by thin film hydration technique and hand shaking method

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ABSTRACT

Objective(s): The aim of present study is to formulate mefenamic acid transdermal gel based on vesicular drug delivery approaches.

Materials and Methods: For the preparation of mefenamic acid transdermal gel, transfersomes were selected as colloidal carriers. Transfersomes were prepared by hand shaking and thin film hydration techniques. The obtained transfersomes were characterized for vesicular diameter, zeta potential, drug content, entrapment efficiency and *in vitro* diffusion studies.

Results: Among Different formulations of transfersomes, T10(prepared by thin film hydration and containing soya lecithin: span60 ratio 1:2) was considered as the best formulation because of its mean vesicular diameter of 369 nm, zeta potential of -14 mV, drug content of 99.6%, entrapment efficiency of 84.4%, and sustained drug release of 93.3% after 12 h.T10 formulation was incorporated into gel. Comparative study was made among plain gel, and transfersomal gel. Among these two gels, transfersomal gel considered as best because of its highest drug content (91%), spreadability (43.5 g.cm/sec), pH (6.9) and sustained drug release profile for 12 h.

Conclusion: By comparing hand shaking and thin film hydration techniques, it was found thin film hydration technique produced better results and transfersomal gel was indicated better results than plain gel.

Keywords: *Entapment efficiency, Mefenamic acid, Stability, Transfersomes, Vesicular diameter*

INTRODUCTION

Transdermal route offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter-and intra-patient variations, and most importantly, it provides patients convenience [1,2].

In the last few years, the vesicular systems have been promoted as a mean of sustained or controlled release of drugs.

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These vesicles are preferred over other formulations because of their specific characteristics such as lack of toxicity, biodegradation, capacity of encapsulating both hydrophilic and lipophilic molecules, capacity of prolonging the existence of the drug in the systemic circulation by encapsulation in vesicular structures, capacity of targeting the organs and tissues, capacity of reducing the drug toxicity and increasing its bioavailability [3, 4].

The transdermal route of drug delivery has gained great interest of pharmaceutical research, as it circumvents number of problems associated with oral route of drug administration. Recently, various strategies have been used to augment the transdermal delivery of bioactive molecules. Mainly, they include electrophoresis, iontophoresis, chemical permeation enhancers, microneedles, sonophoresis, and

vesicular system like liposomes, niosomes, elastic liposomes such as ethosomes and transfersomes. Among these strategies, transfersomes appear promising.

A novel vesicular drug carrier system called transfersomes is composed of phospholipid, surfactant, and water for enhanced transdermal delivery. Transfersomes are a form of elastic or deformable vesicle, which were first introduced in the early 1990s.

Transfersomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self-optimized and ultra-flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. The vesicular transfersomes are more elastic than the standard liposomes and thus well suited for the skin penetration.

Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum [5, 6]. Mefenamic acid (MA) is non-steroidal anti-inflammatory drug (NSAIDS) that exhibits anti-inflammatory and analgesic activities. It is a BCS class-2 drug. It is available as tablets, capsules and suspension forms. MA has a wide range of gastrointestinal disorders, like gastrointestinal bleeding and gastric upset. It has poor solubility over the pH range of 1.2-7.5.

The biological half-life of MA is 2 to 4 h. MA causes the COX1 and COX2 inhibitions.

By inhibiting COX1 receptors, it causes severe gastric bleeding and peptic ulcers. By inhibiting COX2 receptors it causes severe cardiovascular side effects. Because of short half-life, frequent administration of the drug is required which may lead to missing the dose of the drug. Hence, formulating mefenamic acid loaded ethosomes and transfersomes can minimize the dose and dosing frequency and side effects.

There is no transdermal formulation of mefenamic acid available till date as per literature review [7, 8].

MATERIALS AND METHODS

Mefenamic acid was purchased from Sigma Aldrich Chemicals Pvt. Ltd., Bangalore),ý soya lecithin was obtained from HIMEDIA Laboratories Pvt. Limited, Mumbai. Span60 , chloroform , ethanol , and methanol were purchased from SD fine-chem. Limited, Mumbai, India.

Preparation of mefenamic acid transfersomes by modified hand shaking technique

Required quantities of soya lecithin and surfactant were taken into a round bottom flask and dissolved in a mixture of 2:1 ratio of chloroform and ethanol by shaking. The thin film was formed by rotary evaporation by using rotary evaporator for 15 minutes at 25 ^{0}C, 600 mm/hg pressure and 100 rpm. Vacuum is applied for one hour to dry the film. Mefenamic acid was dissolved in 10 ml 7.4 pH phosphate buffer which was heated to 55 ^{0}C. Then, the film was hydrated with the heated buffer by hand shaking for half an hour.

Then, the mixture was stirred for half an hour in orbitary shaker. Next, the transfersomes were observed under microscope.

Transfersomal suspension was stored in refrigerator at 4 ^{0}C. Five formulations were prepared using different concentrations of soya lecithin and by varying the soya lecithin: span60 ratio [9].

Preparation of mefenamic acid transfersomes by thin film hydration technique

Required quantities of soya lecithin and surfactant were taken into a round bottom flask and dissolved in a mixture of 2:1 ratio of chloroform and ethanol by shaking.

The thin film was formed by rotary evaporation by using rotary evaporator for 15 minutes at 25 ^{0}C, 600 mm/hg pressure and 100 rpm. Vacuum is applied for one hour to dry the film. Mefenamic acid was dissolved in 10 ml 7.4 pH phosphate buffer which was heated to 55 ^{0}C.

Then, the film was hydrated with the heated buffer by rotaevaporator for half an hour. Then, the mixture was stirred for half an hour in orbitary shaker. Next, the transfersomes were observed under microscope.

Transferosomal suspension was stored in refrigerator at 4 ^{0}C.

Composition of transfersomes are given in Table 1. Five formulations were prepared using different concentrations of soya lecithin and by varying the soya lecithin: span60 ratio [10, 11].

Table 1. Composition of transferosomal formulations

Formulation Code	Soya Lecithin: Span60 Ratio	CHCl$_3$:C$_2$H$_5$OH Ratio	Mefenamic acid (mg)
T1, T6	1:1	2:1	50
T2, T7	1:1.5	2:1	50
T3, T8	1.5:1	2:1	50
T2, T9	2:1	2:1	50
T5, T10	1:2	2:1	50

RESULTS AND DISCUSSION

Mefenamic acid loaded transfersomes using modified hand shaking method Optical Microscopy

Morphology was determined for 5 formulations using optical microscopy (S-3700N, Hitachi, Japan). The photo micrographic pictures of the preparation was obtained from the microscope by using a digital SLR camera [12].

Fig .1. Photomicrographic images of T2 formulation of mefenamic acid loaded transfersomes prepared by hand shaking technique
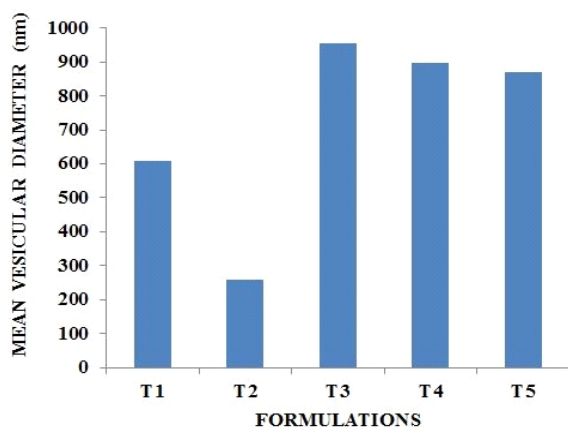
Vesicular diameter

The five prepared formulations were characterized for mean vesicular diameter using Zetasizer (Malvern Instruments Ltd). The analysis was performed at a temperature of 25 $^\circ$C with double distilled water as dispersion medium [13].

All five formulations were in nano size range. The mean vesicular diameter of T1, T2, T3, and T4 and T5 formulations was found to be 609 nm, 259.3 nm, 993.4 nm, 881 nm and 874 nm, respectively.

Among all formulations, T2 formulation showed minimum vesicular diameter of 259.3 nm.

Zeta potential

The prepared five formulations were characterized for zeta potential value in order to know the stability of the formulations.

The analysis was performed at a temperature of 25°C with double distilled water as dispersion medium [14].

Fig. 2. Comparison of mean vesicular diameter of five formulations of mefenamic acid transfersomes prepared by modified hand shaking technique
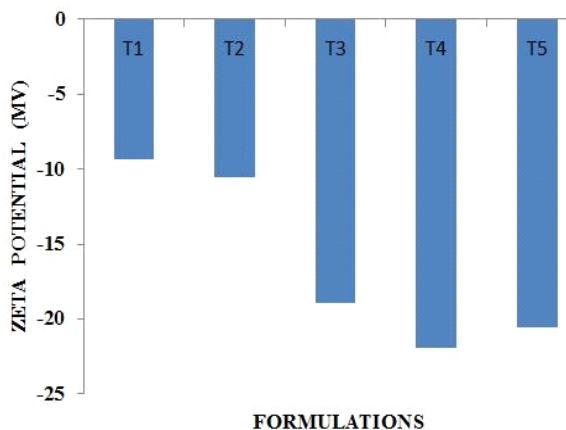

Fig. 3. Comparison of zeta potential values of five formulations of mefenamic acid transfersomes prepared by modified hand shaking method

From the results, it was found that all formulations were stable. The zeta potential values of T1, T2, T3, T4 and T5 formulation was found to be 9.36 mV, -13.1 mV, -18.9 mV, -21.9 mV and -20.6 mV, respectively. Among all formulations, T4 formulation showed greater stability.

Drug content

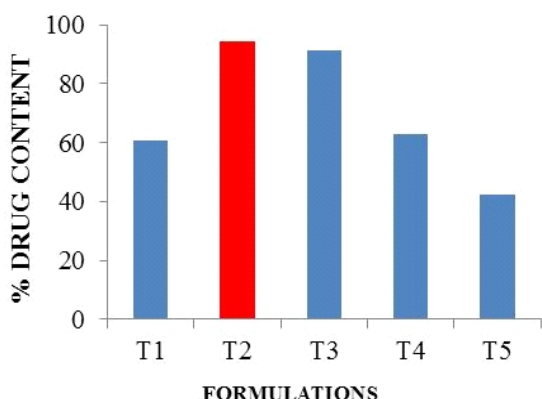The prepared five formulations were evaluated for drug content [15].

Fig. 4. Comparison of drug content among five formulations of mefenamic acid loaded transfersomes prepared by modified hand shaking technique

Drug content of T1, T2, T3, T4 and T5 formulations was found to be 60.62, 94.36, 91.17, 62.79 and 42.47%, respectively. Out of five formulations, the highest drug content was observed for 1:1.5 ratio of phospholipid to surfactant in formulation T2 with 94.36%.

Encapsulation efficiency

All five formulations were evaluated for drug entrapment efficiency using cooling ultracentrifuge (Eltek, Mumbai) [16, 17]. The percentage of drug entrapment efficiency of T1, T2, T3, T4 and T5 formulations was found to be 82.09, 84.39, 76.33, 84.07and 82.47%, respectively. The highest percentage of entrapment efficiency was obtained for 1:1.5 ratio of phospholipid to surfactant in formulation T2. The transfersomes prepared using soya lecithin: span60 1:1.5 ratio showed higher entrapment efficiency. By increasing the surfactant concen- tration, entrapment efficiency decreased which may be due to the fact that decrease in the entrapment efficiency with increasing surfactant ratio

above a certain limit/concentration can disrupt the regular linear structure vesicular membranes.
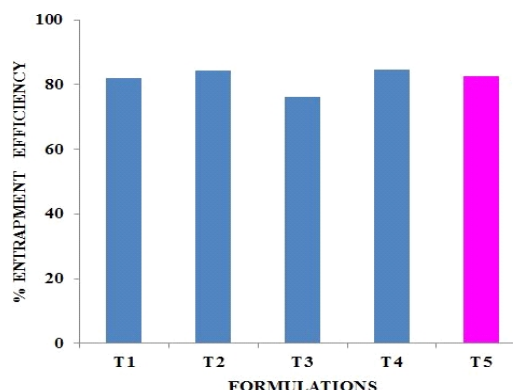

Fig .5. Comparison of drug entrapment efficiency among five formulations of mefenamic acid loaded transfersomes prepared by modified hand shaking method

Comparison of in vitro drug diffusion study of mefenamic acid loaded transfersomes

All five formulations were evaluated for in vitro drug diffusion studies using Franz diffusion cell [18,19]. In vitro drug release studies were conducted for a time period of 12 h as indicated in Fig 6.
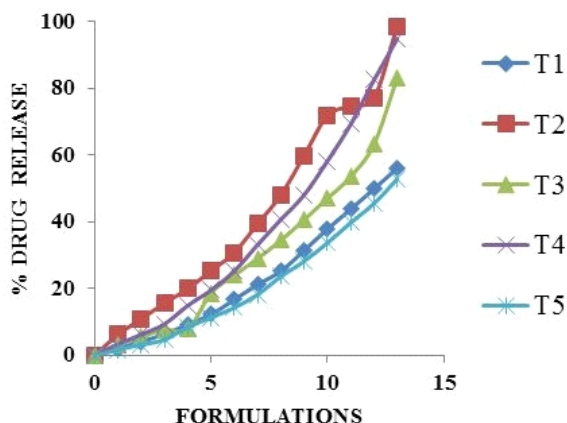

Fig. 6. Comparison of in vitro drug diffusion studies among five formulations of mefenamic acid loaded transfersomes prepared by modified hand shaking technique

It was observed that formulation T2 of 1:1.5 ratio of soya lecithin to span60 showed a sustained release profile of 98.72% up to 12 h when compared to other formulations.In transferosomal formulations, the results showed that the rate of drug release depended on the percentage of drug entrapment efficiency.

From 5 transfersomal formulations tested, T5 showed a better sustained drug release than other formulations. Hence, it was further optimized as best transfersomal formulation.

Meffenamic acid loaded transfersomes by the film hydration technique
Optical microscopy

Morphology was determined for all 5 formulations using optical microscopy (S-3700N, Hitachi, Japan)[20]. The micrographic pictures of the preparations were obtained from the microscope using a digital SLR camera.

Fig .7. Photomicrographic images of T10 formulation of mefenamic acid loaded transfersomes prepared by thin film hydration technique

Vesicular diameter

The prepared five formulations were characterized for vesicular diameter using Zetasizer (Malvern Instruments Ltd). The analysis was performed at a temperature of 25 °C with double distilled water as dispersion medium.
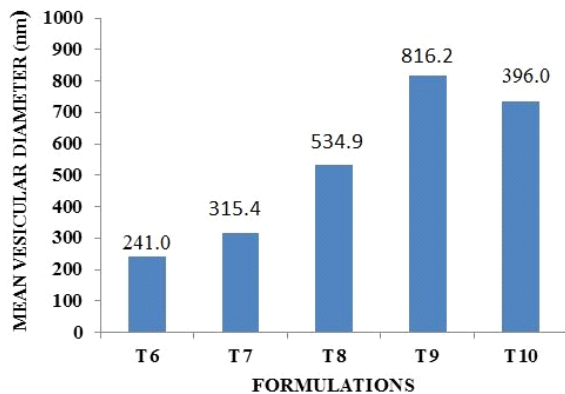

Fig. 8. Comparison of mean vesicular diameter of five formulations of mefenamic acid transfersomes prepared by thin film hydration technique
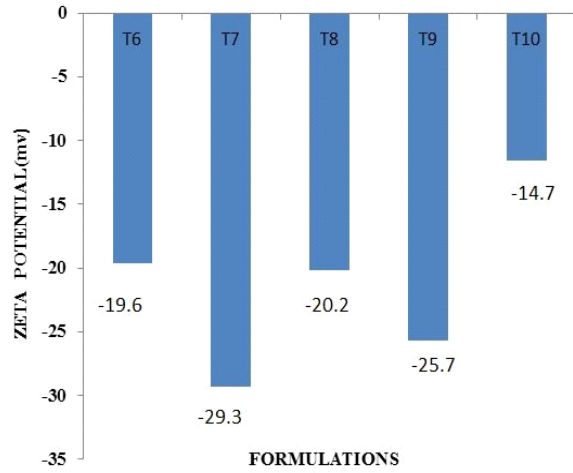

Fig .9. Comparison of zeta potential values of five formulations of mefenamic acid transfersomes prepared by thin film hydration technique

All formulations were found to be stable. The zeta potential values of T6, T7, T8, T9 and T10 formulations were found to be -19.6 mV, -29.3 mV, -20.2 mV, -25.7 mV and -14.7 mV, respectively. Among all formulations, T2 formulation showed highest stability.

Drug content

The prepared five formulations were evaluated for drug content as indicated in Fig 10 [23].

Drug content of T6, T7, T8, T9 and T10 formulations was found to be 78.94, 91.26, 86.91, 69.25 and 99.6%,
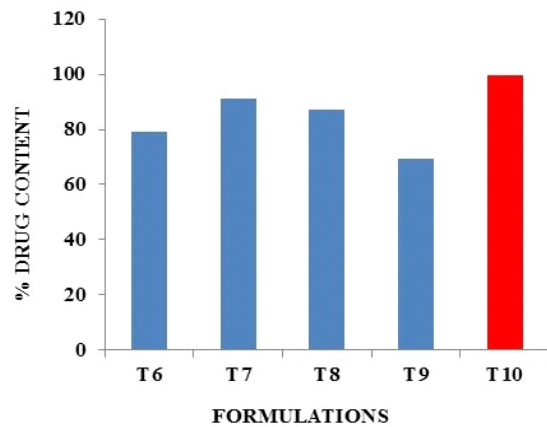

Fig. 10. Comparison of drug content among five formulations of mefenamic acid loaded transfersomes prepared by thin film hydration technique

respectively. Among five formulations tested, the highest drug content was observed for 2:1 ratio of phospholipid to surfactant used in formulation T10 with 99.6%.

Encapsulation efficiency

All five formulations were evaluated for drug entrapment efficiency using cooling ultracentrifuge (Eltek, Mumbai) [24].
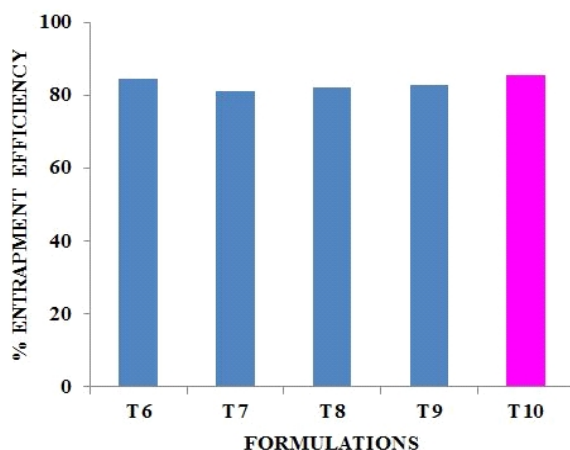

Fig. 11. Comparison of drug entrapment efficiency among five formulations of mefenamic acid loaded transfersomes prepared by thin film hydration technique

The percentage of drug entrapment efficiency of T6, T7, T8, T9 and T10 formulations was found to be 84.39, 81.04, 82.13, 82.96 and 85.54%, respectively. The highest percentage of entrapment efficiency was observed for 2:1 ratio of phospholipid to surfactant used for the preparation of formulation T10.

The transfersomes prepared using soya lecithin: Span60 2:1 ratio showed higher entrapment efficiency. With increasing the surfactant concentration, entrapment efficiency decreased which may be attributed to the fact that decrease in the entrapment efficiency with increasing surfactant ratio above a certain limit/concentration can disrupt the regular linear structure vesicular membranes.

Comparison of in vitro drug diffusion of mefenamic acid loaded transfersomes

All five formulations were evaluated for in vitro drug diffusion studies using Franz diffusion cell [25]. In vitro drug release studies were conducted for a time period of 12 h as shown in Fig 12.
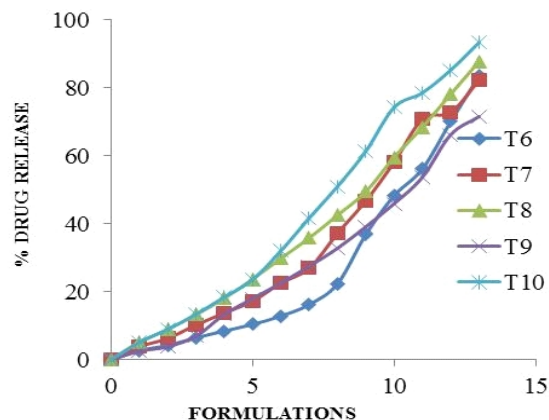

Fig. 12. Comparison of in vitro drug diffusion among five formulations of mefenamic acid loaded transfersomes prepared by thin film hydration technique

From the data, it was observed that T10 formulation composed of 2:1 ratio of soya lecithin to Span60 showed a sustained release profile of 93.31% up to 12 h when compared to other formulations.

In transfersomal formulations, the results indicated that the rate of drug release depended on the percentage of drug entrapment efficiency.

From 5 transferosomal formulations tested, T10 formulation showed a more sustained drug release than other formulations.

Hence, it was further optimized as best transfersomal formulation.

Comparison of hand shaking and thin film hydration techniques

Transfersomes were prepared by two methods of modified hand shaking and thin film hydration techniques.

By comparing the two techniques, it was evident that thin film hydration technique generated better reesults because of its minimum vesicle diameter, good stability, highest drug content, entrapment efficiency and more sustained in vitro drug release.

Kinetic models for optimized formulation

Several plots (zero order, first order, Higuchi and Peppas plots) were drawn for the optimized formulation in order to determine the release kinetics and drug release mechanism as shown in Table 2.

Table 2. Kinetic data of T10 transfersomal formulation

Time (h)	% Cumulative drug release	Drug remaining (%)	Log of % drug remaining	T ½	Log T	Log % cumulative drug release
0.5	5.056	94.95	1.977	0.707	-0.30	0.703
1	8.931	91.07	1.959	1	0	0.950
2	13.36	86.64	1.937	1.414	0.30	1.125
3	18.43	81.57	1.911	1.732	0.477	1.265
4	23.55	76.45	1.883	2	0.602	1.371
5	32.03	68	1.832	2.236	0.698	1.505
6	41.64	58.36	1.766	2.449	0.778	1.619
7	50.97	49.03	1.690	2.645	0.845	1.706
8	61.32	38.68	1.587	2.828	0.903	1.787
9	74.22	25.78	1.411	3	0.954	1.870
10	90.67	9.4	0.973	3.162	1	1.957
11	93.31	6.69	0.82	3.316	1.041	1.969
12				3.464	1.079	

Table 3. Kinetic data obtained for T10 formulation

Formulation	Zero order Plot (R^2)	First order Plot (R^2)	Higuchi Plot (R^2)	Peppas plot(n)
T10	0.9683	0.9081	0.7762	0.9399

Table 4. Composition of different formulation of gel

Ingredients	Formulation code		
	PG	FE5	FT10
Ethosomes/ transferosomes		1% w/v	1% w/v
Carbopol 934	1 g	1 g	1 g
Triethanolamine	q.s	q.s	q.s
Propylene glycol	10 ml	10 ml	10 ml
Methyl paraben 0.5%	0.2 ml	0.2 ml	0.2 ml
Propyl paraben 0.2%	0.1 ml	0.1 ml	0.1 ml
Distilled water	Up to 100 ml	Up to 100 ml	Up to 100 ml

From the obtained results, it was concluded that the drug release followed a zero order kinetics and was fitted into Korsmeyer equation revealing non fickian diffusion mechanism.

Formulation of transfersomal gel

Plain gel (PG) and nano-based gels (T10G) were prepared by simple dispersion technique and evaluated visually for clarity.

Evaluation of transfersomes loaded gel
Clarity

Plain gel (PG) and nano-based gels (T10G) were prepared by simple dispersion technique and evaluated visually for clarity and the results are shown in Table 5.

The results clearly indiv=cated that all formulations were clear.

pH measurement

The formulated plain gel (PG) and nano-based gels (T10G) were evaluated for pH values and the results are given in Table 6.

Table5. Clarity results of PG and T10G formulations

Formulations	Clarity
PG	+++
T10G	++

Table 6. pH evaluation of PG, and FT10 formulations

Formulations	Ph
PG	6.8
T10G	7

The pH of PG, E5G and T10G were found to be 6.8, 6.9 and 7, respectively.

Homogeneity

All gel formulations were found to be homogenous and free of aggregates.

Grittiness

All the formulations were found to fulfil the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

Drug content

The % drug content of PG and T10G formulations were evaluated.

The percent of drug content of PG and T10G formulations were found to be 94.2% and 91%, respectively indicating that T10G formulation had the highest drug content of 91%.

Spreadability

The formulated plain gel (PG) and nano-based gels (T10G) were evaluated for spreadability and the results are given in Table 7.

The highest spreadability of 44.50 g.cm/sec was obtained for FT10G formulation.

Table 7. Spreadability results of PG, E5G and T10G formulations

Formulations	Spreadability
PG	23.53 g.cm/sec
T10G	44.50 g.cm/sec

In vitro diffusion studies

All five formulations were evaluated for *in vitro* diffusion release study using Franz diffusion cell for a period of 12 h.

The cumulative drug release of PG and T10G formulations were found to be 97.8% and 89.4%, respectively after 5 h and 12 h respectively. T10G formulation exhibited a more sustained release compared to other formulations which can be attributed to the higher drug content and greater entrapment efficiency. The results are presented in Table 8.

The kinetics parameters were obtaind using different plot and it was observed that optimum formulation (FT10) followed first order release with non-fickian diffusion mechanism.

CONCLUSIONS

Five formulations of transfersomes were prepared by either hand shaking or thin film hydration methods by varying the phospholipid to surfactant ratios.

All formulations were characterized for vesicular diameter, zeta-potential and evaluated for drug content, entrapment efficiency and in vitro diffusoin studies.

T10 formulation with the composition of phospholipid: surfactant 2:1 ratio was found to be best formulation. In the process of transfersomes preparation, different parameters such as

Table 8. In vitro release kinetic data of T10G formulation

Time (h)	% Cumulative drug release	Log % remaining	T ½	Log T	Log % cumulative drug release
0.5	9	1.95	0.707	-0.30	0.95
1	14.5	1.93	1	0	1.16
2	22.6	1.88	1.414	0.30	1.35
3	31.3	1.83	1.732	0.477	1.49
4	39.8	1.77	2	0.602	1.59
5	45	1.74	2.236	0.698	1.65
6	55	1.65	2.449	0.778	1.74
7	59.8	1.6	2.645	0.845	1.77
8	64	1.5	2.828	0.903	1.8
9	68.9	1.49	3	0.954	1.83
10	71.4	1.47	3.162	1	1.85
11	74.2	1.41	3.316	1.041	1.87
12	79	1.32	3.464	1.079	1.89

Table 9. Kinetic parameters determined from the in vitro drug release kinetic plots

Formulation	Zero order plot (R^2)	First order plot (R^2)	Higuchi plot(R^2)	Peppas plot (n)
T10G	0.917	0.990	0.887	0.645

phospholipid: surfactant ratio, hydration tempe-rature, heating temperature were optimized.

The best formulations of transfersomes (T10) was incorporated into 1% carbopol gel base by simple dispersion method. The formulated gels were evaluated for clarity, pH, drug content, spreadability, viscosity and in vitro diffusion studies. Among the plain gel and transferosomal (GT10) gels tested, transfersomal gel showed the best results compared to plain gel.

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CONFLICT OF INTEREST

The authors report no declaration of interest.

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