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A COMPARISON STUDY OF LIPOSOMES, TRANSFERSOMES AND ETHOSOMES BEARING LAMIVUDINE

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ABSTRACT: The aim of this study was to compare the skin permeation of liposomes, transfersomes and ethosomes of lamivudine under non-occlusive conditions. The liposome and transfersomes prepared by thin film hydration method and ethosomes were prepared by slight modification on hot method. The Liposomal formulation (LP1) ethosomal formulation (ET2) and transfersomal (TF2) formulation showed highest entrapment 49.76 ± 2.1%, 81.97 ± 1.5% and 83.81 ± 1.4%, optimal nanometric size range 515 ± 4.6 nm, 374 ± 8.9nm and 315 ± 8.5nm and smallest polydispersity index0.529±0.019,0.432± 0.011 and 0.422± 0.009 respectively. The results of skin fluorescence experiments showed that penetration depth and fluorescence intensity of calcein from ethosomes and transfersomes was much greater than that from liposomes. Stability studies indicated that there was no significant physical change in vesicular formulation for 45 days at different temperatures. The *in vitro* result indicates that liposome retrain on the surface of skin due to poor permeation power, transfersomes improve penetrates of lamivudine and made drug easiest to accumulate in the skin. Ethosomes enhances permeation the drug to the deeper layer of skin and enter into systemic circulation rather than skin deposition. Transferosomes and ethosomes are able to cross the stratumcorneum and permeate drug to deeper tissue compare to liposomes.

INTRODUCTION: Controlled drug delivery into a body is one of the major topics in pharmaceutical research. Optimum therapeutic is not restricted to only proper drug selection but also effectual drug delivery.[1-3] The application of medicinal substances to the skin is a concept undoubtedly as old as humanity, the Papyrus records of ancient Egypt describes a variety of such medication for external use [4].

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The skin represents a moderately large and readily accessible surface area for absorption, the application is a non-invasive procedure that permits a continuous intervention, and it is possible to terminate the absorption preventing overdose or undesirable effects. Equalled with the traditional oral administration route, transdermal delivery shows surplus advantages: it minimizes the first-pass metabolism, it circumvents drug degradation under the extreme acidity of the stomach, it precludes inconsistent delivery due to food interactions, and it provides more controlled delivery [1-5].

The best avenue to improve drug penetration and/or localization is obviously to manipulate the vehicle or to utilize a drug carrier concept [5-8]. The use of

liposome as magic bullet for treatment many diseases was concept raised by Paul Ehrlich and Bangham. Liposomes were small lipid vesicles containing water, can entrap hydrophilic or lipophilic drugs in its system. Liposomes were used as transdermal and topical drug delivery system for many drugs for treating locally or systemic diseases. Liposomes offer many advantages as drug delivery carriers-for example they are biodegradable, non-toxic, and are able to encapsulate both water-soluble and lipophilic substances.

Conventional liposomes have some disadvantage for its permeation power on stratum corneum barrier to skin, different generation of liposomes were prepared to overcome this barrier effect. Niosomes (1st generation), Transferosomes (2nd generation), Ethosomes (3rd generation) were different generation of flexible liposomes with different mechanism for enhancement of drug to skin.[5-7] Comparison of different vesicular carrier were mentioned in (**Table 1)** with different characteristic features. Transfersomes is 2nd generation of flexible liposomes with combination of phospholipids and edge activator. An edge activator is usually a single chain surfactant that causes the destabilization of the lipid bilayer of the vesicle and increases the vesicle-elasticity or fluidity.[4-6] Transferosomes are ultra deformable or ultraflexible liposomes that easily cross the skin under the influence of a transepidermal water activity gradient. Transferosomes vesicles easily access to stratum corneum of skin in search of aqueous hydration [6-12]. Ethosomes represent 3rd generation of elastic lipid carriers, developed by Touitou [7-12]. Ethosomes is ethanol modified liposomes acts as reservoir systems and offer continual delivery of medication to the desired site. (no paragraph required) carriers, developed by Touitou [7-12].

Ethosomes is ethanol modified liposomes acts as reservoir systems and offer continual delivery of medication to the desired site. Ethosomes are malleable vesicles which act with ethanol effect and lipid penetration; result in releasing of the drugs to the different layer of skin. Ethanol may also provide vesicles with soft flexible characteristics, which allow them to penetrate more easily into the deeper layers of the skin [10-13].

TABLE 1: COMPARISON OF DIFFERENT CHARACTERISTICS OF LIPOSOMES, TRANSFERSOMES AND ETHOSOMES [8]

Characters	Liposome	Transferosomes	Ethosomes
Vesicles	Bilayer Lipid vesicle	2nd generation elastic lipid vesicle carriers	3rd generation elastic lipid vesicle carriers
Composition	Phospholipids and Cholesterol	Phospholipids and edge activator	Phospholipids and Ethanol
Characteristics	Microscopic Spheres (Vesicles)	Ultraflexible Liposome	Elastic Liposome
Flexibility	Rigid in nature	High deformability due to surfactant	High deformability and elasticity due to ethanol
Permeation Mechanism	Diffusion/Fusion/Lipolysis	Deformation of vesicle	Lipid Perturbation
Extent of Skin Penetration	Penetration rate is very less as the stiff shape and size does not allow to pass through stratum corneum	Can easily penetrate through paracellular space by flexible structure	Can easily penetrate through paracellular space by ethanol effect
Route of administration	Oral, Parenteral. Topical and transdermal	Topical and Transdermal	Topical and Transdermal
Marketed products	Ambisome, DaunoXome, Doxil, Abelect	Transfersomes® (Idea AG)	Nanominox, Cellutight EF, Noicellex, Decorin Cream

Vesicular carrier as transdermal route has been loom for enhancing the drug through the skin. For treatment of HIV/AIDS effective antiretroviral remedy is required on a long term basis to supress the virus and lessens the disease progression. Lamivudine is nucleoside analog reverse transcriptase inhibitor (NRTI) class of antiretroviral drug used to avert and treat HIV/AIDS. Lamivudine has short biological half-life which requires frequent dosing. For management of HIV, lifelong treatment is required so transdermal drug delivery is best choice of dosage form as it decrease the frequency of dosing and could maintain constant plasma level for prolonged

period of time [4-7]. The aim of the current assessment is to compare different vesicular carrier bearing lamivudine for its potential power to overcome the skin barrier and penetrate the skin.

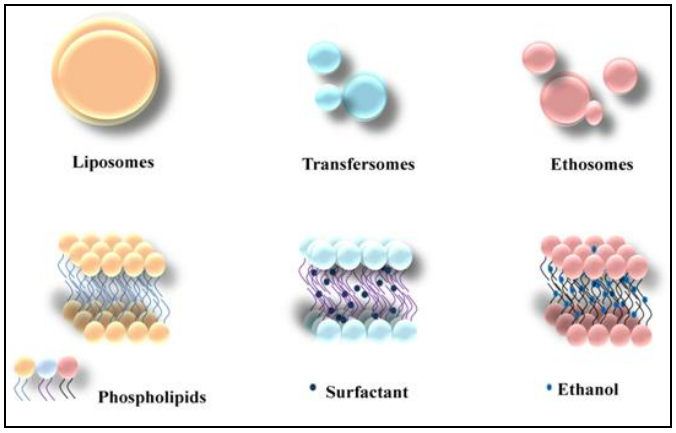

FIG. 1: SCHEMATIC DIAGRAM OF LIPOSOMES, TRANSFERSOMES AND ETHOSOMES

MATERIAL AND METHOD:

Lamivudine is gift sample from Mylan, Hyderabad, Phospholipid 90H was obtained from Lipoid, Germany, Tween, Propylene glycol, ethanol, chloroform were purchased from Himedia, Mumbai, India and other solvents are of HPLC grade from Himedia.

Preparation of Liposomes, Transferosomes and Ethosomes:

Liposomes and transferosomes were prepared by using a film-hydration method, ethosomes using a slight modification on hot method [14-15].

Liposomes and transfersomes were prepared by rotary evaporator using film hydration method. The composition of liposomes and transferosomes were mentioned in (**Table 2**) and phospholipid, surfactant, drug/fluorescent dye (carboxy fluorescein) and organic solvent were added in round bottom flask and attached to rotary evaporator maintained temperature at 60°C. After thin film formation, add aqueous buffer to the phospholipid mixture and kept overnight for swelling of the phospholipid sheet with agitation and temperature at 60°C. Ethosomes were prepared by hot method in which it consists of phospholipids, ethanol, lamivudine/fluorescent dye and aqueous phase. (**Table 2**) In a vessel, add ethanol in which phospholipid (soybean derived phosphatidylcholine) and lamivudine/Fluorescent dye mixed with continue stirring and maintained to temperature of 60°C. In separate vessel aqueous phase/ PBS 7.4 is heated to 60°C. The ethanolic mixture is added to the PBS mixture with continuous stirring at 800rpm for 30 minutes. All vesicles formulations are kept at 4-8°C for optimum stability.

Percentage Drug Entrapment:

Ultracentrifugation method has been used to estimate the entrapment efficiency of drug in liposome, transfersomes and ethosomes. Vesicles formulations are centrifuged at 15000 rpm for 4 hours in cool centrifuge and superannuated liquid is decanted and centrifugation is repeated for 3 cycles. All superannuated liquid are collected into volumetric flask and diluted with suitable solvent and the concentration of drug/lamivudine is estimated at 271nm in all samples [7, 15].

Entrapment efficiency =

{(Total concentration of drug –amount of drug in clear supernatant fluid)/Total concentration of drug} x100

Size and Zeta Potential determination:

Zeta potential and size of vesicles were analysed by dynamic light scattering method (DLS), (Malvern Zetamaster, UK), 100 microliter of the liposome, transfersome, ethosomes was diluted with 900 µL deionized water in cuvettes cell. At least three independent samples were prepared, each of which was measured at least three times [7].

TABLE 2: COMPOSITION OF DIFFERENT VESICULAR CARRIER BEARING LAMIVUDINE

Formulation code	Liposomal formulation	Transfersomal formulation		Ethosomal formulation	
	LP_1	TF_1	TF_2	ET_1	ET_2
Phospholipid (mg/ml)	100mg	100mg	100mg	100mg	100mg
Cholesterol (mg/ml)	10mg	10mg	10mg	10mg	10mg
Ethanol (%)	-	30	40	-	-
Tween 80(mg/ml)	-	-	-	10	30
Propylene glycol (%)	-	10%	10%	-	-
Buffer	qs	qs	qs	qs	qs

Skin Permeation Study:

Formulations are selected on the basis of entrapment efficiency and vesicles size was subjected to skin permeation study. The skin permeation ability of vesicular formulations (ET_2, TF_2 and LP_1) was confirmed by fluorescence study. The fluorescent labelling will be carried out by preparing the optimized selected formulations with fluorescence marker carboxyfluorescein. Selected formulation (ET_2, TF_2 and LP_1) loaded fluorescent marker will be applied topically on dorsal surface of rat skin. After post application of formulation, the rats will be sacrificed and dorsal skin will be detached, cut into small pieces, fixed into fixative solution (3:1, absolute alcohol: chloroform) for 4 hours. The dorsal skin kept in ethanol for 30 minutes and thereafter in mixture of ethanol and xylene for 60 minutes. The skin wax blocks were prepared for microtomes section. The skin wax sections will be observed under a fluorescence microscope for permeation of fluorescent probe [7, 5, 17, 19].

***In-vitro* release study:**

All animal trials were performed according to the protocol standard by the Institutional Animal Ethics Committee (IAEC Reg No. 1227/ac/08/CPCSEA) of Smriti college of Pharmaceutical education, Indore. The *in vitro* release study is carried out using diffusion cell. All vesicular formulations were studied using the rat dorsal surface as membrane for *in vitro* release study. The diffusion cell consists of donor compartment and receiver compartment, the rat skin is placed between the compartments which act as membrane for drug permeation of drug. The temperature and stirring was monitored and maintained in receptor cell at 37±0.5°C and 120 rpm respectively. Vesicular formulation is placed in donor compartment and phosphate buffer pH 7.4 is filled in receiver compartment and at regular interval withdraw 1ml of sample from diffusion cell and replace with fresh buffer PBS 7.4 to maintain skin condition. The withdrawn sample was analysed spectroscopic method at 271nm [7, 15].

HPLC assay:

The quantity of drug diffused in the receiver compartment during *in vitro* skin permeation, stability studies, entrapment efficiency experiments are analysed by RP-HPLC using methanol: water: acetonitrile (70:20:10 v/v) at flow rate of 1ml/min (Waters HPLC). The samples were analysed using photo diode array detector at 271nm.[15]

Stability Studies:

The entrapment efficiency, particle size and physical appearance of the vesicular suspension are prudent indicators of the kinetic stability of vesicular formulation. The particle size and entrapment of vesicular formulation were measured and 10 mL each of the formulations was stored at 4-8°C, room temperature (25±2°C) and physiologic temperature (37±2°C). At specific time intervals of 15, 30, and 45 days, the samples were taken and particles size, entrapment efficiency and physical appearance was examined [15, 16-18].

RESULT AND DISCUSSION:

Sometimes an active pharmaceutical ingredient needs more than a simple formulation to become a successful drug. Liposomes were used as carrier for many drugs, conventional liposomes lacks some benefits which arise in modification of liposomes and different generation of liposomes were evolved. Transfersomes which is edge activator liposomes are well known for its ultra-deformable liposomes and ethosomes as ethanolic liposomes are combination of ethanol and phospholipid effect. Transfersomes and liposomes prepared by film hydration method and ethosomes were prepared by hot method with some modification.

All formulation were analysed for its entrapment efficiency and result revealed that 49.76±2.1 (LP), 65.56±1.3 (TF-1), 81.97±1.5 (TF-2), 63.52±0.8 (ET-1), 83.81±1.4 (ET-2) percentage respectively. (**Table 3**) In transfersomes, as the concentration of edge activator increases the entrapment efficiency increases. TF-2 has shown more entrapment then TF-1 formulation. Ethosomes formulation consist of ethanol from 10-30%, ET-2 formulation has shown higher entrapment than ET-1 due to high ethanol concentration. Ethanol makes the phospholipid membrane flexible and retains the drug in the core of vesicles. Increasing the ethanol concentration from 10 to 30% enhances the entrapment of drug in vesicles. Liposomes have poor entrapment efficiency than all other formulation due to non-flexibility of membrane.

The descending order of entrapment efficacy is ET-2>TF-2>TF-1>ET-1>LP. ET-2 and TF-2 has shown more entrapment efficiency than all other formulations. Particles size of vesicles has paramount importance in permeation of drugs. The smaller the particles size, the higher the permeation rate of drug to deeper tissue due to its surface area and small size. The size of the all formulation was in range of 300-550 nm. Liposomes have shown larger size than other formulation whereas the transfersomes (edge activator liposomes) and ethosomes (ethanolic liposomes) have smaller size of particles. (**Table 3**) The existence of surfactant in transfersome led to modification of the surface charge of the vesicle, which may affect the vesicular characteristics like size of the particle and high amount of ethanol presences in ethosomes also help in reduction of size of the vesicles [17-19].

TABLE 3: CHARACTERIZATION OF LIPOSOMES, TRANSFERSOMES AND ETHOSOMES

Formulation Code	Liposomal formulation	Transferosomal formulation		Ethosomal formulation	
	LP_1	TF_1	TF_2	ET_1	ET_2
Size in nm	515 ± 4.6	395±12.5	374 ± 8.9	365 ± 8.5	315 ± 8.5
% Entrapment Efficiency	49.76±2.1%	65.56± 1.3%	81.97±1.5%	63.52±0.8%	83.81±1.4%
Zeta Potential (ζmv)	−3.2 ± 3.7	−10.2 ± 4.1	−21.5 ± 1.6	−12.2 ± 3.9	−39.2 ± 3.9
Polydispersity Index	0.529	0.507	0.432	0.407	0.422

The fluorescence skin study reveals that transfersome and ethosome were able to permeate the stratum corneum and reaches to deeper layer of skin whereas liposomes retain in the epidermis of skin.[19-22] Transfersome able to permeate the skin with help of edge activator which squeeze through channels in the stratum corneum and transferosomes up to 500 nm can cuddle through to permeate the stratum corneum barricade spontaneously.[19] Ethosomes due to the ethanol effect, where ethanol interrelates with the lipid molecules in the polar head group region causing in a drop in the transition temperature of the lipids in the stratum corneum, increasing their fluidity and decreasing the density of the lipid multilayer.[16, 20] Due to the flexibility and blend of ethosomes with skin lipids, ensuing in the release of the drug into the dermis layers of the skin [23-26]. In **Fig. 2**, photograph of fluorescence skin histology reveals that ethosomes and transfersomes able to penetrate the fluorescent probe into the deeper layer of skin.

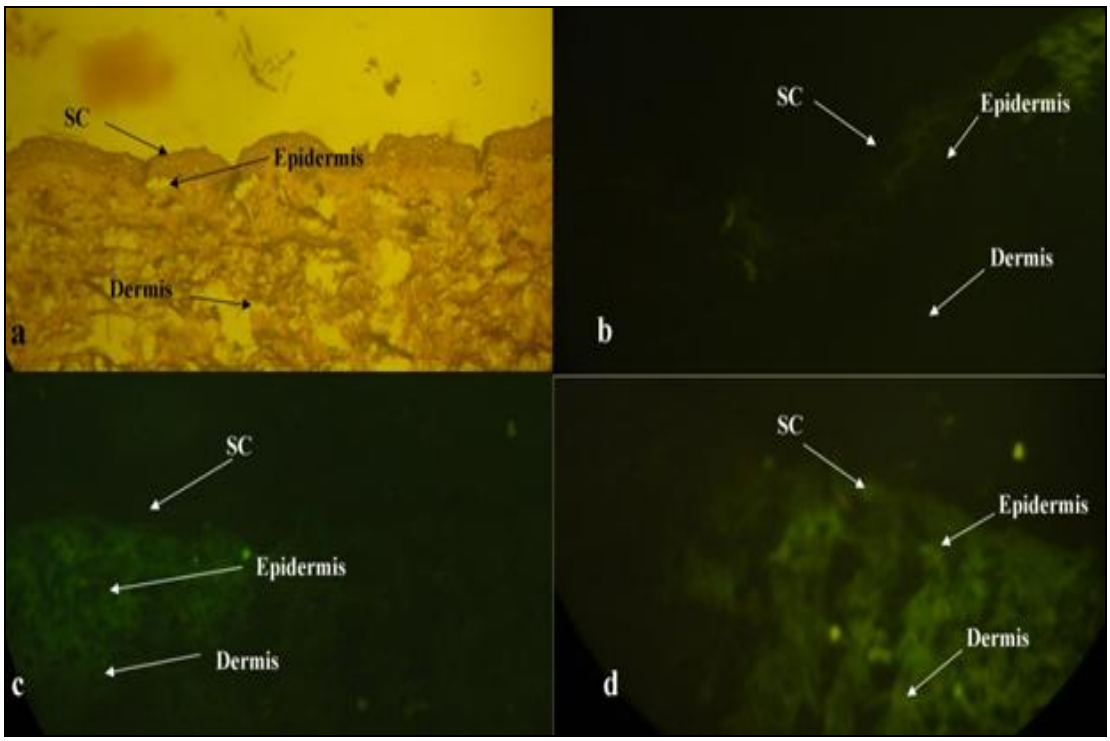

FIG.2: SKIN FLUORESCENCE STUDY OF CONTROL SKIN (a), LIPOSOMES (b), TRANSFERSOMES (c) AND ETHOSOMES (d)

In vitro release of lamivudine using rat skin as membrane showed that ethosomal and transfersomal formulation have release above 50% of drug TF-1(69.62±2.34%), TF-2 (82.12±1.26%), ET-1 (65.42±1.43%) and ET-2 (89.61±1.75%) for 12 hours whereas liposomes release LP (36.32±2.43%) 12 hours whereas liposomes release LP (36.32±2.43%) for 12 hr. (**Fig. 3).** The lag time of ET-2 and TF-2 formulation have shown faster and then all other formulation. ET-2 and TF-2 were superior in release and have shown sustained release for 12 hours. The ET-2, TF-2 and LP formulation were selected for stability studies and kept at different temperature for 45 days. The parameters selected for stability studies are particles size, drug entrapment and physical stability.

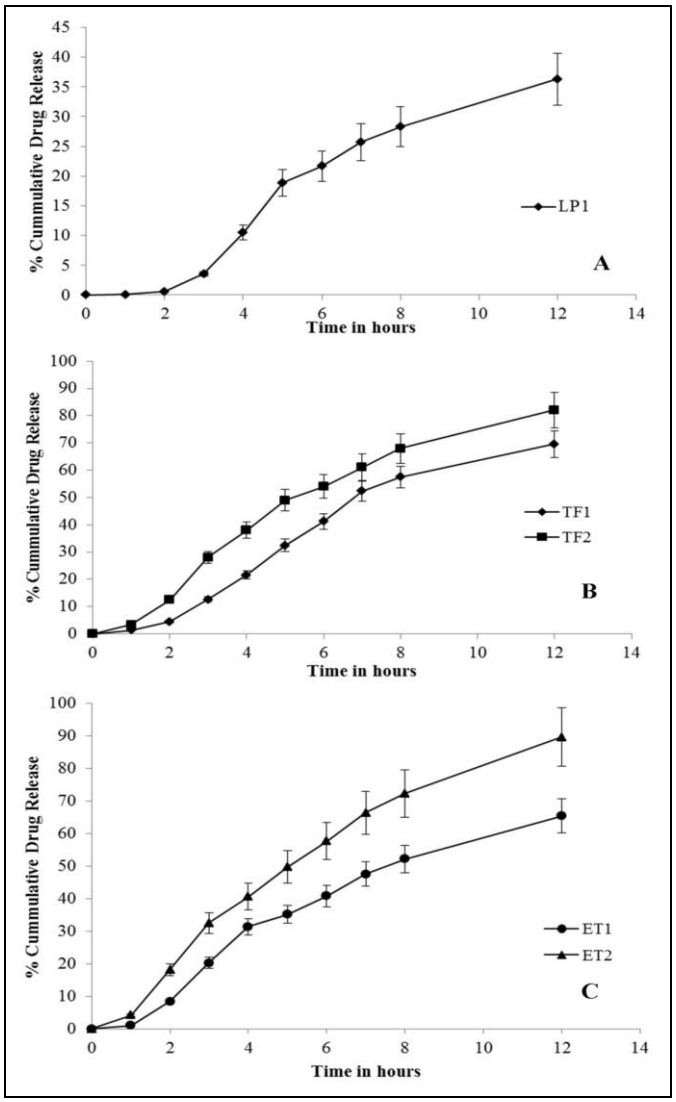

FIG. 3: COMPARISON OF *IN VITRO* RELEASE FROM FRANZ DIFFUSION SKIN PERMEATION STUDY a) LIPOSOME b) TRANSFEROSOMES c) ETHOSOMES

There is no significant change in size of particles in all vesicular formulations. All formulation have shown maintaining in size of vesicles at all temperature for 45 days (**Fig. 4**). Drug entrapment efficiency in vesicles is important parameter for stability of vesicles. Drug leak may occur during storage of vesicles at different temperature.(**Fig. 5**) The liposomes has shown significant decrease in drug entrapment at 37±2°C compared to 4-8°C and 25±2°C. Transfersome and ethosomes have maintained their drug entrapment and no significant Loss of drug kept at all temperature for 45 days.

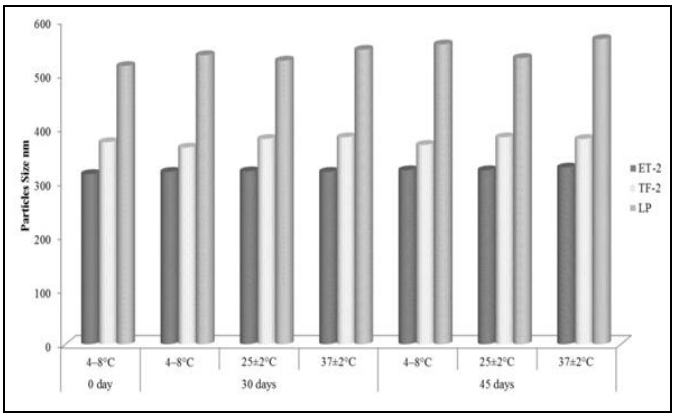

FIG. 4: STABILITY STUDIES OF LIPOSOMES, TRANSFERSOMES AND ETHOSOMES FORMULATION BASED ON PARTICLE SIZE

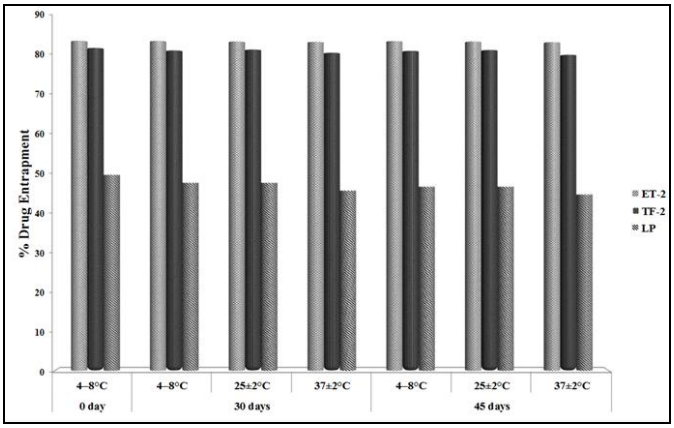

FIG. 5: STABILITY STUDIES OF LIPOSOMES, TRANSFERSOMES AND ETHOSOMES FORMULATION BASED ON PERCENTAGE DRUG ENTRAPMENT

Surfactant helps in stability of vesicles and prevent drug leak during storage. Ethanol provide negative charge to vesicles and these charge prevent aggregation of vesicles and drug leak during storage of vesicles for 45 days at all temperature. There were no physical variations detected up to the 45th day of stability study at the storage condition of 4-8°C and 25±2°C. However, when stored at 37±2°C for 45 days, there was an

observable change in drug content of liposomes (44.76±0.418% at day 45 compared with (44.76±0.41 %at day 45 compared with 49.76±0.25% at day 0), indicating that the prepared liposomal formulation was more stable under refrigeration. In our current investigation different vesicular formulation prepared and evaluated for different parameter and concluded that transfersome (TF-2) and ethosomes (ET-2) were best formulation when compared to liposomes (LP).

CONCLUSION: Flexible (Ethosomes) and ultra-deformable liposomes (transfersomes) well known for its permeation of drugs into skin, utilizing the flexibility and deformability it abridged the lag time of drugs penetrating into skin and enhance deeper penetration into skin. The 2nd and 3rd generation liposomes have high encapsulation, lower particles size and high stability. *In vitro* drug release studies through rat skin showed sustained delivery of lamivudine from transfersomal and ethosomal formulation. Ethosomes and transfersome considerably enhanced the skin penetration of lamivudine in vitro through rat skin when compared to liposomes. Lamivudine vesicular formulation enhances the permeation of drug to deeper skin layers and systemic circulation which required to attain the therapeutic response in HIV treatment.

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CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

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