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Original Article

FORMULATION AND EVALUATION TRANSDERMAL DRUG DELIVERY SYSTEM OF GEMIFLOXACIN

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ABSTRACT

Liposomes are lipid vesicles and one of the most suitable drug delivery systems to deliver thedrug to the target organ and minimize the distribution of the drug to non-target tissues. Liposomes can enhance drug absorption achieved through their ability to come into intimate contact with the adjacent surfaces. The aim of the study the gel formulation of Liposome Contain Dapsone effectively maintains concentrations of active agents to the deep layers of the skin and/or the systemic circulation. In this study an attempt has been made to formulate a gel for dermal therapy of Dapsone. The gel formulated consists of the Dapsone loaded liposomes were prepared by lipid film hydration method with required modifications after optimizing formulation variables. In present work, liposomal and marketed gels showed antibacterial activity against Propionibacterium acnes with maximum zone of inhibition lying in the range of 18 to 26 mm. On comparison of formulated liposomal gel with marketed gel of Dapsone, liposomal gel showed greater percentage of inhibition of bacterial infection against Propionibacteriumacnes. In present in-vivo anti-acne activity was selected as a standard drug and showed the effect of, Formulation- I (marketed Gemifloxacin) and formulation II (liposomalgel LF2) on acne and mean thickness compared to the normal

.

It was observed that formulation-I (marketed Gemifloxacin gel) and formulation-II (liposomal gelLF2) showed a significant reduction in the acne without necrosis as compared with the standard. Various antibiotics like tetracycline, & erythromycin etc. and other drugs like benzoyl peroxide are used for acne treatment. The various draw backs for synthetic drugs are different side effects and resistant developed towards these drugs. Formulation therapy is required to overcome the above draw backs & treat the acne.

***Key words**: Gemifloxacin, Liposomes,Transdermal drug delivery, Propionibacterium*

INTRODUCTION

The name liposome is derived from two Greek words ‘Lipid’ meaning fat and‘Soma’ meaning body. Structurally, liposomes are concentric bilayer vesicles in which anaqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed ofnatural or synthetic phospholipids. The polar character of the liposomal core enables polardrug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized with in the phospholipid bilayer according to their affinity towards the phospholipids. Liposomes are lipid vesicles and one of the most suitable drug delivery systems to deliver the drug to the target organ And minimize the distribution of the drug to non-target tissues. Liposomes can enhance drug absorption achieved through their ability to come into intimate contact with the adjacent surfaces.

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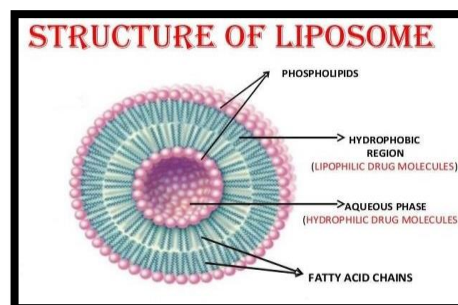
Dapsone is a compound similar to vitamin A. It helps the skinWtorenewitself more quickly and may improve the appearance and texture of skin. The brand of Dapsone cream is used to reduce the appearance offine wrinkles on the face, mottled light and dark skin patches on the face, and benign facial



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lenities (non-cancerous freckles) in adults and adolescents who are at least 17 years old.

The special capacity of liposomes to ensnare drugs both in an aqueous and a lipid stage make such conveyance frameworks alluring for hydrophilicand hydrophobic medications. On account of headways in the strategies for setting up a dplanning liposome, high- capture efficiencies are feasible for fusing drugs into liposomes, making a gigantic drugs way.

Innovative exploration in liposomal drugs has prompted commercialization of a few anticancer therapeutics, for example,

Doxil, Myocet, two liposome based anti-cancer medications; doxorubicin; and an antifungal medication plan, Am Bisome, which is a liposomal definition of amphotericin B utilized for foundational treatment. Liposomes may have a utilization in quality conveyance to address gene-associated messes or for anti body treatment.

METHODOLOGY

Formulation Design:

Preparation of Liposome

Liposomes were prepared by lipid film hydration method (Mansoori et al., 2012). By using rotary vacuum evaporator with modifications. Drug (DAP): SPC: CHOL ratio was altered and vesicle size and drug en trapment efficiency were studied. Briefly, achloroform: methanol (2:1) mixture of different ration of drug (DAP): SPC: CHO Levaporator under vacuum at 400±0.50C to form a lipid film on the wall of a roundbottom flask. The resulting lipid film was then hydrated with PBS (pH 7.4) for 2 hoursat 370±0.50C. The preparation was sonicated at 40C in 3 cycles of 30 sec. and rest of 2 minutes between each cycle by using probe Sonicator. The formulation was homogenized at 15,000 psi pressure in 3 cycles using high-pressure homogenizer to get liposome.

Table1: Composition of liposome on the Basis of Regular 23 Design

Run	Bach No	Lecithin	Cholestrol	RotationSpeed(rpm)
1	**TL1**	**100**	**20**	**200**
2	**TL2**	**100**	**50**	**200**
3	**TL3**	**200**	**20**	**100**
4	**TL4**	**200**	**20**	**200**
5	**TL5**	**200**	**50**	**200**
6	**TL6**	**100**	**20**	**100**
7	**TL7**	**100**	**50**	**100**
8	**TL8**	**200**	**50**	**100**

Evaluation of liposome

Vesicle size determination: Vesicle size was determined using the particle size a nalyzer (Malvern Master Sizer, Malvern Instruments Ltd., Malvern, UK).

Entrapment efficiency: Dapsone was estimated in liposome by ultra-centrifugation method. Liposomal suspension was transferred to 10 ml centrifuge tube. This suspension was diluted with distilled water upto 5 ml and centrifuged at 2000 rpm for 20 minutes. By this we can separate undissolved drugintheformulation.Suitablevolumeoftheprotaminesolutionwa saddedWtotheresultingsupernatant and retained for10 minutes.

Transmission Electron Microscopy: Surface morphology was determined by TEM,f or TEM a drop of the sample was placed on a carbon-coated copper grid and after 15min it was negatively stained with 1% aqueous solution of phosphotungustic acid. The grid was allowed to air dry thoroughly and samples were viewed on a transmission electron microscopy (TEM Hitachi, H-7500 Tokyo, Japan) Nagarsenker et al., 1997) On the basis of results obtainedfromWthestudyTL6wasselectedasoptimizedformulation

Preparation of Gels

Preparation of Carbopol gel base: Carbopol 934 (0.5 g) was weighed and dispersed in 100ml distilled water with mild stirring and allowed to swell for 24 hours to obtain 0.5% gel. Later 2ml of glycerin was added to the gel for maintaining consistency Preservatives (methyl Paraben and Propyl Paraben) also added into the gel. Similarly, 1 and 2% Carbopol gels were prepared (Patel,et.al, 2011)

Table 2: Composition of different gel base

Formulation	CarbopolW(%)
LF1	**0.5**
LF2	**1.0**
LF3	**2.0**

Preparation of liposomal gels: Liposome formulation (weight equivalent to 10 mg) was dissolved in 10ml of ethanol and centrifuged at 6000rpm for 20minutes to remove the unentrapped drug. The supernatant was decanted and sediment was incorporated into the gel vehicle (Pateletal.,2001). The incorporation of the Dapsone loaded liposomes (equivalent to 0.1%) into gels was achieved by slow mechanical mixing at 25rpm W(REMI type BSstirrer, Vasai, India) for 10minutes.The optimized formulation was in corporate into three different gel concentration 0.5, 1 and 2%w/w.

Evaluation of Gel

Determination of pH: Weighed 50 gm of each gel formulation were transferred in 10ml of beaker and the pH was determined using digital pH meter. pH of the topical gel formulation should be between 3–9 to treat the skin infections (Bhalariaetal.,2009).

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Spreadability: The Spreadability of liposomal gel formulation was measured on the basis of slip and drag characteristics of the gels. An apparatus was modified and fabricated which consisted of two glass slides, the lower one was fixed to a wooden plate and the upper one was attached by a hook to a balance. The Spreadability was determined by using the formula: S=ml/t, where S, is Spreadability, mis weight in the pantied to upperslide and t is the time taken to travel a specific distance and l is the distance traveled. For the practical purpose the mass, length was kept constant and 't'was determined(Seraetal.,2006). The measurement of Spreadability of each formulation was done in triplicate and the average values are presented (NiyazBashaetal.,2011).

Measurement of viscosity: The viscosity of gels was determined by using a Brookfield viscometer (DV-IImodel). AT-Barspindle in combination with a helipath stand was used to measure the viscosity and have accurate readings (NiyazBashaetal.,2011).

RESULTS AND DISCUSSION

Table 3: Calibration curve of the proposed method for the estimation of Gemifloxacin

Calibration Curvein 7.4 pH Buffer				
Concentration (µg/mL)	**Absorbance at 254nm**			
	1	**2**	**3**	**Average**
0	**0**	**0**	**0**	**0.000**
2	**0.211**	**0.222**	**0.224**	**0.219**
4	**0.395**	**0.395**	**0.395**	**0.395**
6	**0.565**	**0.568**	**0.565**	**0.566**
8	**0.718**	**0.717**	**0.717**	**0.717**
10	**0.913**	**0.912**	**0.917**	**0.914**

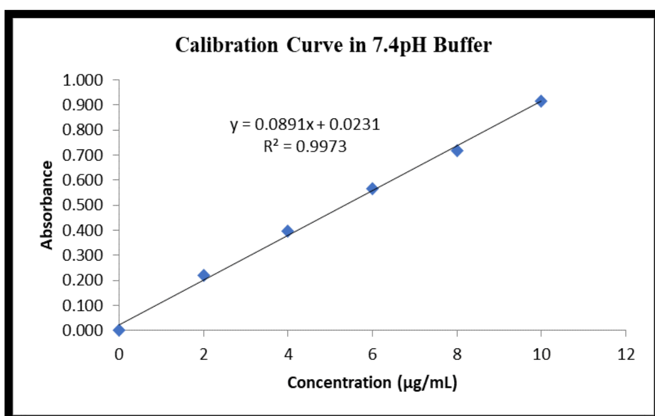


Figure 2: Calibration curve of Dapsone in PBS (pH7.4) at 351nm

Fourier-Transform Infra-Red Spectroscopy (FTIR): The spectrum of drug was authenticated by FTIR spectroscopy. The characteristic peaks present are obtained due to specific structural characteristics of the drug molecule were noted. The FTIRs can of drug are shown in Figure3.

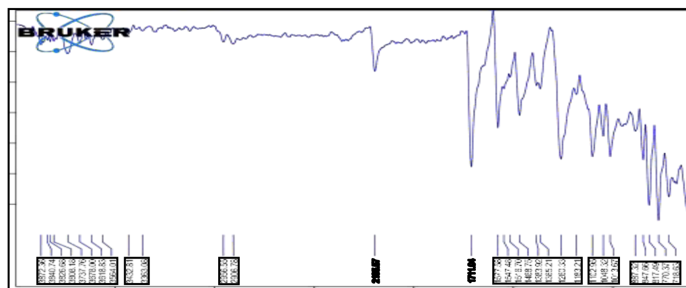
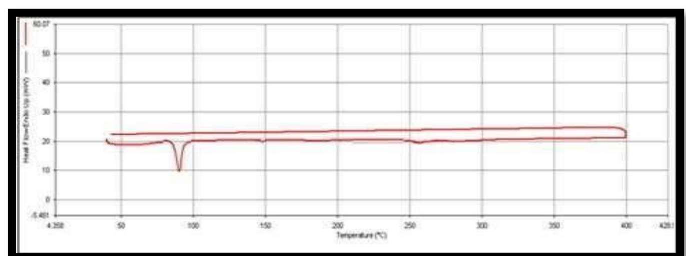
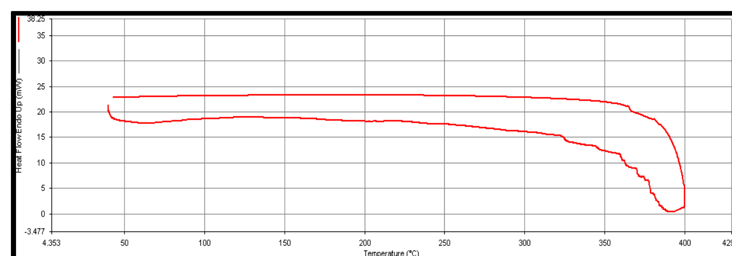


Figure2: FT-IR Spectrum of Pure DRUG

Drug-Excipients compatibility study:





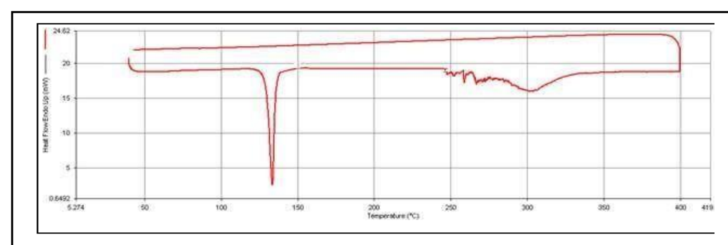


Fig 3: DSC thermogram of (a) Gemifloxacine, (b)cholesterol, (c) Drug+all

Solubility studies of Delfloxacin in different solvent

Solvent	Solubility(mg/mL)			
	1	**2**	**3**	**Average**
0.1NHCl(0.1NHCl)	**1.2**	**0.8**	**0.8**	**0.9**
pH4.5AcetateBuffer	**5.6**	**4.5**	**5.6**	**5.2**
pH 6.8 phosphate buffer	**8.5**	**8.6**	**7.8**	**8.3**
Double Distilled Water (pH7.0)	**9.8**	**9.7**	**8.8**	**9.4**

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pH 7.2 phosphate buffer	**10.5**	**11.2**	**12.2**	**11.3**
pH 7.4 phosphate buffer	**11.5**	**13.2**	**13.5**	**12.7**
0.1N NaOH (pH11.0)	**13.5**	**14.5**	**15.6**	**14.5**

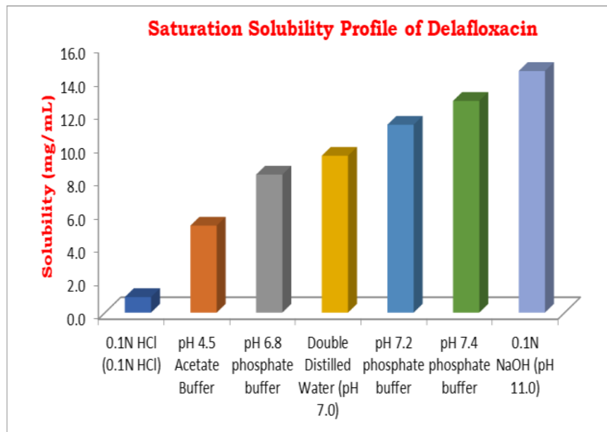
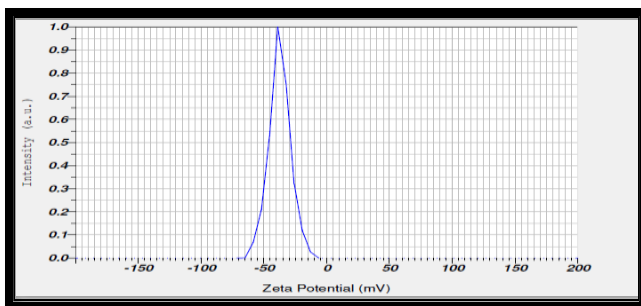


Table 4. Evaluations of Liposomal Formulations of Regular 23 Design

Formulation	Vesiclesize(nm)	ZetaPotential(mV)	Entrapmentefficiency(%)	PolydispersityIndex (PDI±S)
TL1	**165.3**	**-32.1**	**56.73±0.73**	**0.411**
TL2	**256.7**	**25.9**	**55.43±1.48**	**0.229**
TL3	**478.3**	**26.5**	**60.11±0.82**	**0.321**
TL4	**405.1**	**18.7**	**62.52±2.21**	**0.232**
TL5	**552.8**	**-32.8**	**64.87±1.54**	**0.301**
TL6	**180.4**	**-37.5**	**69.10±1.52**	**0.221**
TL7	**319.3**	**29.2**	**66.27±2.00**	**0.839**
TL8	**800.2**	**30.4**	**65.79±1.12**	**0.628**

Study of Zeta Potential



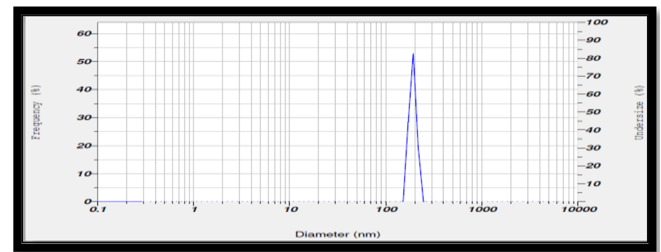


Fig 4: Results of Zeta Potential

Study of vesicle size

Transmission Electron Microscopy: Transmission electron microscopy was performed on electron microscope (TEM Hitachi H-7500 Tokyo, Japan) and photomicrograph was taken at suitable magnification. Photomicrographs how n in figure 6. The TEM characterization revealed that the liposomes are small, spherical vesicles. However, some variation in size distribution was observed, which might be attributed to an uncontrolled charge neutralization process involved between oppositely charged chains occurring during the formation of liposome. TEM revealed that liposomes are in range of 100 to 200nm with a mean size of 180nm.

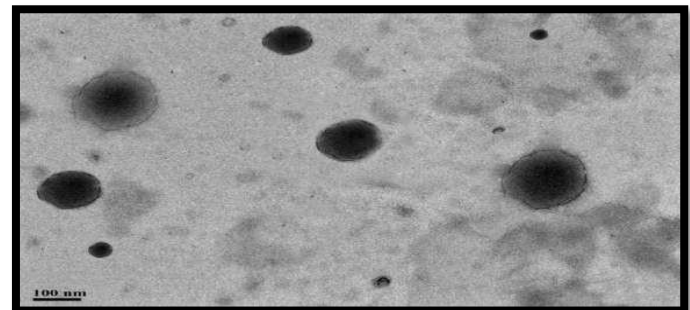
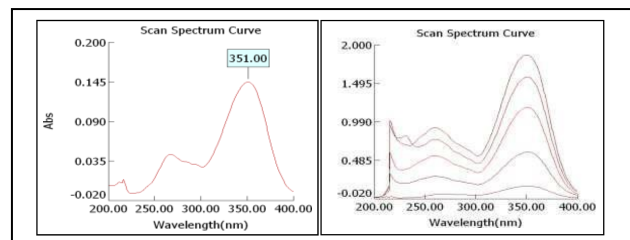


Fig 5: Results of vesicle size

Evaluation of liposomal gel

Drug content

Results of method development and validation Determination of λmax of Delafloxacine



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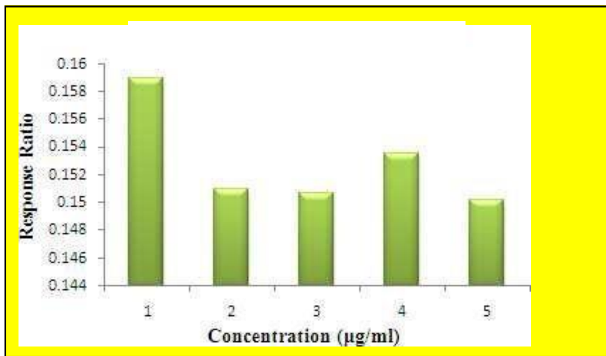

Fig 5: Response Bar graph of Gemifloxacin

5. Results of liposomal gel formulations

Code	pH	Spread ability(gm.cm/sec.)	Viscosity(cps)
LF1	7.2±0.024	10.45±0.075	1870±25
LF2	7.0±0.035	12.32±0.042	1895±33
LF3	7.1±0.045	11.75±0.049	1875±21

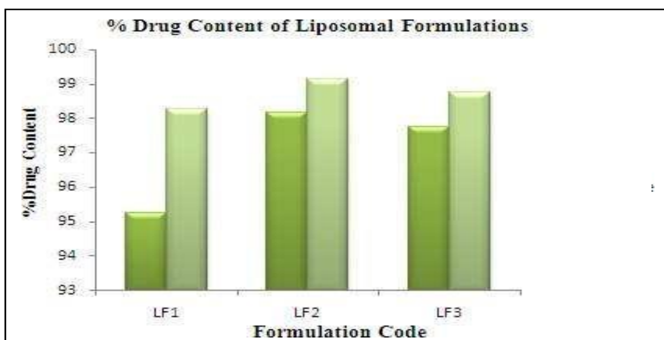

Fig 6: % Drug content of liposomal formulations

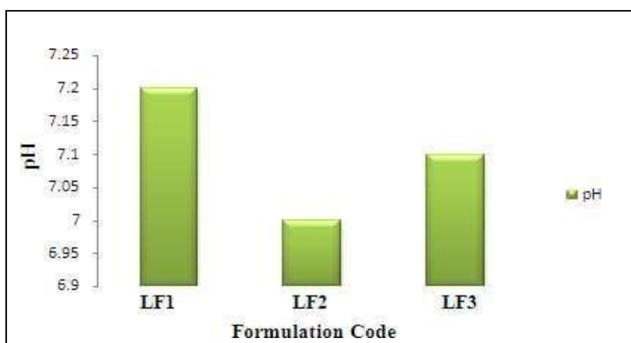

Fig 7: pH of liposomal formulations

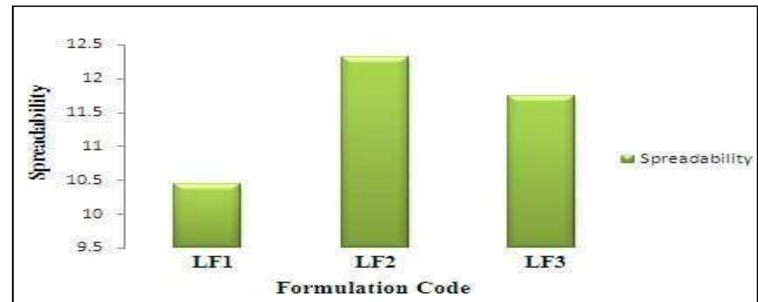

Fig 8: Viscosity of liposomal formulations

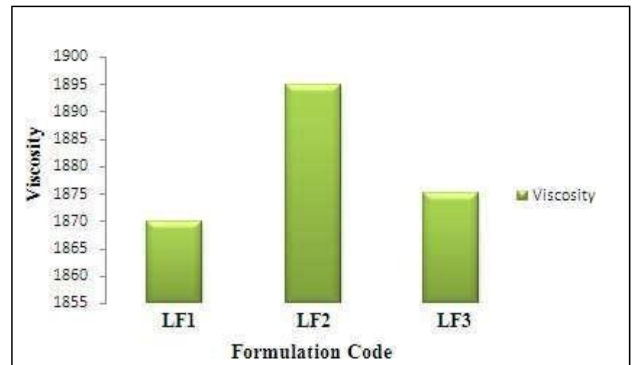

Fig 9: Spreadability of liposomal formulations

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Table 6: In-vitro drug release data for LF1 for Dapsone

Time(h)	Squareroot of Time (h) 1/2	Log Time	Cumulative* % Drug Release	Log Cumulative * %Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	25.450±0.12	1.406	74.55±2.18	1.872
2	1.414	0.301	38.890±0.25	1.590	61.11±1.18	1.786
3	1.732	0.477	55.560±0.14	1.745	44.40±0.88	1.648
4	2.000	0.602	68.890±0.23	1.838	31.11±0.38	1.493
6	2.449	0.778	79.890±0.35	1.902	20.11±0.28	1.303
8	2.828	0.903	85.450±0.21	1.932	14.55±0.08	1.163
12	3.464	1.079	97.080±0.11	1.995	1.22±2.04	0.086

Table 7. In-vitro drug release data for LF2 for Gemifloxacin

Time(h)	Squareroot of Time (h) 1/2	Log Time	Cumulative* % Drug Release	Log Cumulative * %Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	23.450±0.15	1.370	76.55±2.28	1.884
2	1.414	0.301	35.450±0.14	1.550	64.55±1.80	1.810
3	1.732	0.477	50.450±0.25	1.703	49.55±1.48	1.695
4	2.000	0.602	63.450±0.14	1.802	36.55±1.34	1.563
6	2.449	0.778	75.450±0.15	1.878	24.55±0.28	1.390
8	2.828	0.903	84.560±0.36	1.927	15.44±0.16	1.189
12	3.464	1.079	98.120±0.45	1.992	1.88±0.06	0.274

Table 8: In-vitro drug release data for LF3 for Gemifloxacine

Time(h)	Squareroot of Time (h) 1/2	Log Time	Cumulative* % Drug Release	Log Cumulative * %Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	22.250±0.15	1.347	77.75±2.82	1.891
2	1.414	0.301	30.450±0.15	1.484	69.55±1.34	1.842
3	1.732	0.477	42.560±0.15	1.629	57.44±1.28	1.759
4	2.000	0.602	50.560±0.25	1.704	49.44±1.42	1.694
6	2.449	0.778	62.450±0.18	1.796	37.55±1.12	1.575
8	2.828	0.903	68.450±0.45	1.835	31.55±0.42	1.499
12	3.464	1.079	78.890±0.25	1.897	21.11±0.38	1.324

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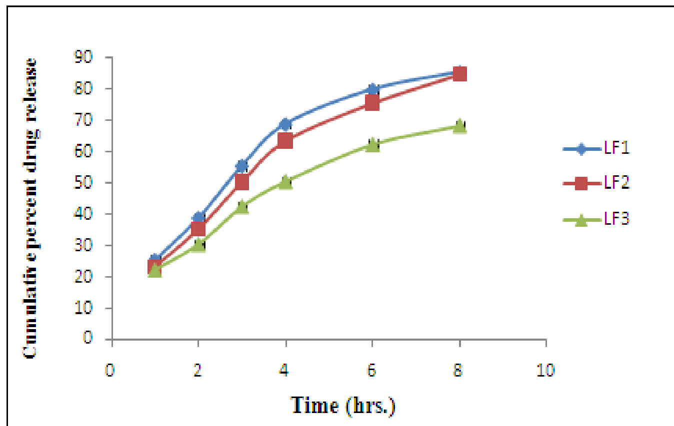

Fig 10: Cumulative % drug released Vs Time

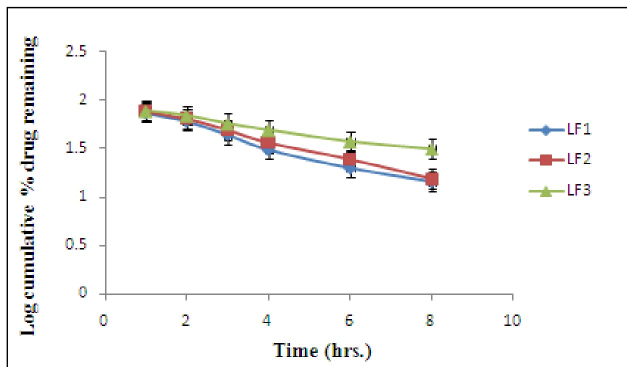

Fig 11: Log cumulative% drug remaining Vs Time

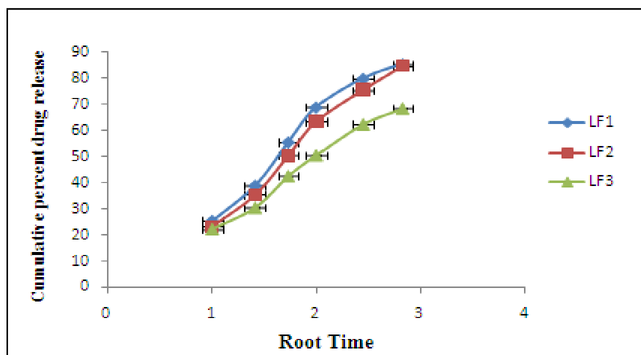

Figure12: Cumulative percent t drug released Vs Squareroot of Time

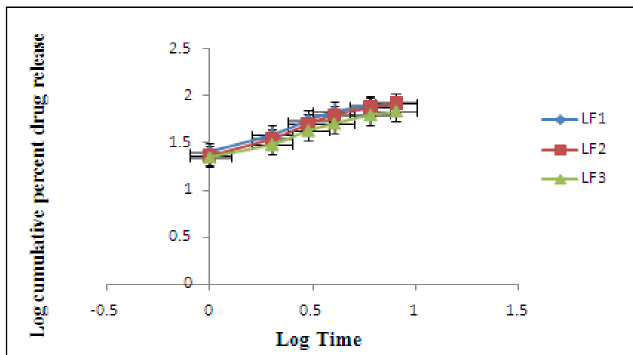

Figure13: Log cumulative percent drug released Vs LogTime

Batch	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas Equation
	R^2	R^2	R^2	R^2
LF1	**0.868**	**0.916**	**0.954**	**0.868**
LF2	**0.906**	**0.940**	**0.976**	**0.906**
LF3	**0.912**	**0.953**	**0.978**	**0.912**

Table 9: Regression analysis data of liposomal gel formulation

In-vitro diffusion study of the liposomal gels (LF1, LF2, and LF3) was performed using modified Franz diffusion cell with dialysis membrane in phosphate buffers pH 6.8 for a period of 12 hours for Dapsone.

In order to determine the exact mechanism of drug release from liposomal gel the in-vitro release data were fitted to Korsmeyer Peppas equation and the 'n' values were calculated. 'n' values were found to be in the range of $0.5<n<1.0$,which suggest that the drug release mechanism from the gel followed non-Fickian diffusion mechanism (Anomalous transport). Liposomal gel released drug in controlled release manner in 12 hours but in case of marketed formulation there is no controlled release of drug from gel.

In vitro drug release data for LF1, LF2 ,and LF3 upto 12hours for Dapsone was found tobe 97.08±0.11,98.120±0.45 and 78.890±0.25 respectively. Percentage cumulative drug (Dapsone) released after 12 hours from LF1, LF2 and LF3liposomal gel formulation was 97.08±0.11, 98.120±0.45 and 78.89±0.25 respectively.

CONCLUSION:

In conclusion it can be proposed that the liposomal gel have proved to be efficient carrier for the Transdermal drug delivery of drug molecules. Liposomes are lipid vesicles and one of the most suitable drug delivery systems to deliver the drug to the target site and minimize the distribution of the drug to non-target tissue. Liposomes can enhance drug absorption achieved through their ability to come into intimate contact with the adjacent surfaces. The developed liposomal gel-based formulation can prove to be very instrumental in the efficient cure of the acne. The formulation an be scaled up for industrial purpose since the same is very simple to prepare. Moreover, since the formulation is a combination of the drugs and hence positive results with rapid cure can be achieved. Ho ever clinical correlation and more evident research may be needed for the same to be utilized for human use in cure of acne.

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