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Research Article

Formulation and evaluation of Lamivudine transferosomal gel

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Abstract

Aim and objective: The aim of the study was to formulate and evaluate Transferosomal gel of lamivudine.

Method:Lamivudine transferosomes was prepared using thin film hydration method taking span 80, Polyoxyethylene lauryl ether in different proportion. the formulation was characterised by UV spectroscopy, FTIR, in-vitro drug release, gel evaluations.

Results: Total nine formulations were formulated and optimised formulation F3 showed entrapment efficiency EE (91.17), %CDR (96.12) and small particle size (98.19 nm). SEM of optimized lamivudine Transferosomes appeared as spherical, well identified, unilamellar vesicles. The optimized formulation of Transferosomes was further formulated to gel with Poloxamer 407 gel 0.5%, 1% and 2% w/w ,HPMC k15, Propylene glycol, DMSO. Among these F3 formulation with Poloxamer 407 2%w/w transferosomal gel is the optimised transferosmal gel and showed Spreadability value 6.01±0.12 cm, pH value 5.01 ±0.47. The actual drug content of the Transferosomal gel was found to be 97.29 ±0.66%, which represents good content uniformity. The viscosity of lamivudine Transferosomal gel is found to 5960 ±0.75cps. The percentage drug release for lamivudine Transferosomal gel is 97.31 %. stability studies showed that Transferosomal gel is more stable at 4°C when compared to other temperatures. The future scope of the study is to perform the *In Vivo* studies to evaluate the potency of the prepared formulation.

Keywords: Lamivudine Transferosomal gel, Transferosomes, Topical, Anti-viral drug, Thin Film Hydration Technique.

1. INTRODUCTION:

Transdermal drug delivery, makes use of human skin as a port of entry for systemic delivery of drug molecules [1]. 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 surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation [2,3]. The word transferosme means “carrying body”, and is derived from the Latin word 'transferre', meaning “to carry across”, and the Greek word “soma”, for a “body” [4,5]. A gel consists of a polymer which swells in the presence of fluid and perhaps within its structure. The rigidity of the gel is determined by the amount of fluid it entraps. These gels are wet and soft and look like a solid material[6].

2. MATERIAL AND METHODS:

2.1 collection of drug and excipients

Lamivudine (Provided by Yarrow chem Pvt. Ltd), Cholesterol, soya lecithin , Span 80 Sodium Cholate, Polyoxyethylene lauryl ether (Brij 35), Poloxamer 407 ,HPMC K15 ,Propylene glycol, DMSO Methanol ,Chloroform, Ethanol.

2.2 Preformulation studies:

Organoleptic properties:

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture

Solubility:

Lamivudine (10mg) was suspended separately in a 10 ml of different solvents at room temperature in tight closed test tube and shaken by wrist action. The samples were filtered through whattman filter paper and diluted appropriately with same solvent and concerntration was determined by UV-VIS spectroscopy.

Melting point:

Determination of melting point of drug was done by capillary method using melting point apparatus.

Determination of absorption maxima

10mcg/mlsolution was taken to determine absorption maxima. Initially blank buffer solution was kept and scanned in the region of 200-300nm. Then sample was kept for analysis and scanned in the same region.

Calibration curve of lamivudine

Preparation of standard stock solution in distilled water

Accurately weighed 10mg of Lamivudine and dissolved in 10ml of distilled water. From this solution 1ml was withdrawn

and diluted to 100ml with distilled water, to produce standard stock solution of Lamivudine (10mcg/ml)

Preparation of sample solution in distilled water

From the working stock solution 0.2ml was taken and added to 10ml of distilled water to make 2 mcg/ml. From these different concentrations were made 2,4,6,8,10mcg/ml. The absorbance was observed at 270 nm respectively using UV visible spectrophotometer (Lab India UV 3000+). Then calibration curve of Lamivudine was plottted as the graph between absorbance value (nm) on Y-axis and concentration (mcg/ml) on X-axis.

Drug – excipient compatibility study: FTIR

FTIR spectrum was taken for pure drug and physical mixture of excipients with drug by potassium bromide pellet method. The samples were analyzed between wave numbers

4000 and 400 cm-1

FORMULATION AND DEVELOPMENT

Formulation development lamivudine loaded transferosomes-rotary film evaporation method

soyalecithin, cholesterol, sodium cholate, span 80, and Brij 35 with different molar ratios were dissolved in 10 mL of a mixture of three organic solvents (Methanol:chloroform:ethanol) at (2:1:2) v/v/v ratio. Using rotary evaporator, thin lipid film on the internal surface of the round-bottomed flask was formed. Lamivudine (100 mg) was dissolved in 20 mL of an isotonic phosphate buffer (pH 6.8). Lamivudine solution was used to hydrate the prepared thin film by rotation at 100 rpm for 2 hours. To form large multilamellar vesicles, the resulting suspensions were kept for 24 hours at 25°C. To form smaller vesicles, the transferosomal dispersions were sonicated for 30 minutes. The Lamivudine transfersomes were separated from the entrapped Lamivudine by high-speed centrifugation at 20,000 rpm for 3 hours at −5°C using cooling ultracentrifuge. To separate the untrapped Lamivudine, clear supernatant was carefully taken out after the centrifugation.

Table 1: Formulation code of preparation of transferosomes

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lamivudine	10	10	10	10	10	10	10	10	10
Cholesterol (mg)	4	4	4	4	4	4	4	4	4
Lecithin	2	2	2	2	2	2	2	2	2
Span 80	5	10	15	-	-	-	-	-	-
Sodium Cholate	-	-	-	5	10	15	-	-	-
Brij 35	-	-	-	-	-	-	5	10	15
Methanol:chloroform:ethanol (mL) (2:1:2)	10	10	10	10	10	10	10	10	10

Preparation of transferosomal gel of lamivudine

Table 2: Composition of Topical Transfersome Gel Formulation:

Formulation code	Ingredients			
	Poloxamer 407 (%)	HPMC k15 (mg)	Propylene glycol	DMSO
F3	0.5	20	10	10
F3	1	30	10	10
F3	2	40	10	10

In brief, in 10 mL distilled water, required quantities of Poloxamer 407 were added slowly and stirred with the help of magnetic stirrer at 50 rpm for 1 hour. To ensure the maximum dissolution of polymers, the prepared solution was left in the quiescent state for 12 hours in a refrigerator. Then, the solution (poloxamer with HPMC k15) was stirred slowly at 5°C for 5 hours until a gel was formed. Various formulations were prepared as shown in Table.

CHARACTERIZATION LAMIVUDINE LOADED TRANSFEROSOMES

Vesicle morphology / vesicle diameter

It can be determined using scanning electron microscopy

Particle Size, Zeta Potential [7,8]:

vesicle size, size distribution zeta potential were determined by dynamic light scattering system by malvern zeta sizer

Polydispersity index [9]

PDI is a measure of heterogenecity of a sample based on size .polydispersity can occur because of agglomeration of sample .PDI can be obtained by dynamic light scattering microscopy(DLS). PDI of less than 0.1 is considered as homogenous and ≥0.4 heterogenous

Entrapment efficiency [10,11]:

The entrapment efficiency was determined by using direct method. Detergents are used to break the transfersome membranes1 ml of 0.1% Triton X- 100(Triton X-100 dissolved in phosphate buffer) was added to 0.1 ml Transfersomes preparations and made up to 5 ml with phosphate buffer then it was incubated at 37°C for 1.5 hrs to complete breakup of the transfersome membrane and to release the entrapped material. The sample was filtered through a Millipore membrane filter (0.25) µm. and the filtrate was measured at 270 nm for Lamivudine. The amount of Lamivudine was derived from the calibration curve. The entrapment efficiency is expressed as:

$$\text{Percentage Entrapment Efficiency} = \frac{\text{Amount entrapped}}{\text{Total amount added}} \times 100$$

TRANSFERSOMES GEL EVALUATIONS

Physical appearance:

The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

PH of formulation[12,13]**:**

Weighed 50 gm of gel formulation were transferred in 10 ml of beaker and measured it by using the digital pH meter. pH of the topical gel formulation should be between 4-6 to treat the skin infections.

Determination of viscosity

Viscosities of the gels were determined by using Brookfield Viscometer (model- RVTP). Spindle type, RV-7 at 100 rpm

Spreadability[13,14]**:**

A modified apparatus suggested was used for determining spreadability. the spreadability was measured on the basis of slip and drag characteristics of the gels. the modified apparatus was fabricated and 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 spread ability, m is weight in the pan tied to upper slide and t is the time l is the distance traveled. for the practical purpose the mass, length was kept constant and't' was determined.

Drug content[13,15]**:**

1 gm. of the prepared gel was mixed with 100 ml. of water aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 270 nm. drug content was calculated by linear regression analysis of the calibration curve.

***In-vitro* diffusion study**[14,15]**:**

an in-vitro drug release study was performed using modified franz diffusion cell. dialysis membrane (hi media, molecular weight 5000 daltons) was placed between receptor and donor compartments. transferosomal gel lamivudine was placed in the donor compartment and the receptor compartment was filled with phosphate buffer, ph 6.8 (24 ml). the diffusion cells were maintained at 37±0.5°c with stirring at 50 rpm throughout the experiment. at different time interval, 5 ml of aliquots were withdrawn from receiver compartment through side tube and analyzed for drug content by uv visible spectrophotometer and analyzed spectrophotometrically at 270 nm using phosphate buffer pH 6.8 as blank.

Stability studies [14,15]: Both formulations were stored in screw capped, amber colored small glass bottles at 4 ±1°C and 28 ± 1°C.

(a) Effect of storage temperature on vesicle size: Subsequent change in vesicle size of the formulations stored at 4±1°C and 28 ± 1°C was determined using a Zetasizer (Malvern Instrument, UK) after a period of 7,14, 21 and 28 days.

(b) Effect of storage temperature on drug content:After storage for a specified period of time of 7, 14, 21and 28 days, the drug content of both the formulations was determined. Drug content in transfersomes gel was determined spectrophotometrically to indirectly estimate the amount of drug entrapped in gel.

4. RESULTS AND DISCUSSION

4.1 Preformulation Studies:

a. Organoleptic properties

Table 3: Organoleptic Properties Of Lamivudine

S.no	Parameter	Drug characteristics
1	Color	White
2	Odour	Odourless
3	Taste	Tasteless
4	Appearance	Amorphous Powder

b. Melting point determination:

Table 4: Melting point determination of lamivudine

Reported Melting Point	Observed Melting Point
160-162^{0}c	161^0 c

Observation: the melting point of lamivudine observed melting point was found to be 161ºc . this indicates the purity of drug sample. any impurity if present will cause variation in the melting point of given drug substance.

c. Solubility results

Table 5: solubility of lamivudine

Solvent	Solubility Of Lamivudine
Water	39±0.78
Methanol	40 ±0.06
Phosphate Buffer 6.8	43±0.05
Phosphate Buffer 7.4	34.5±0.04

Observation: Lamivudine was found to be soluble in methanol and phosphate buffer(6.8ph) and soluble in water , soluble in Hcl .

4.2 UV-Spectroscopy-Analysis of Drug

Determination of lambda max of lamivudine in phosphate buffer 6.8 by uv spectoscopy.

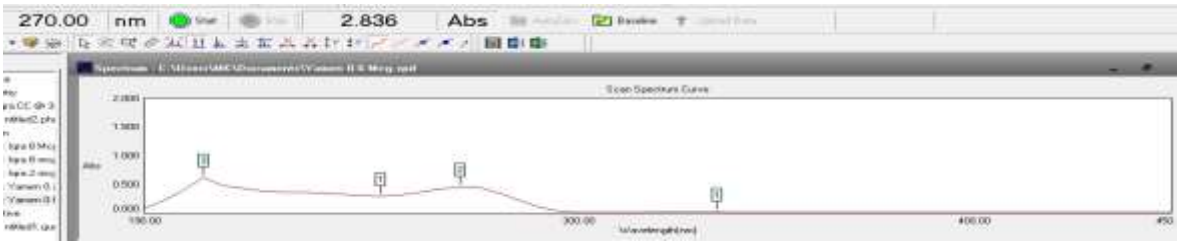


Figure 1: Lamda max determination of lamivudine

Solution of lamivudine concentration of 10 ug/ml was scanned in the range of wavelength 200-300 nm.The absorption spectrum was found to be sharp and maximum at wavelength of 270nm , therefore , it was selected as the wavelength for detection in phosphate buffer pH6.8

e. Calibration curve:

Table 6: calibration curve data of lamivudine in phosphate bufferph6.8 .

Concentration (µg/ml)	Absorbance
0	0.000 ±0.00
2	0.178 ±0.065
4	0.342 ±0.017
6	0.509 ±0.089
8	0.684 ± 0.101
10	0.847 ±0.154

SD±(n=3)

R2 value was found to be 0.9998 and shows the slope of 0.0851 in methanol indicate that it obeys beer's lambert's law in concentration range of 2-10 µg/ml. The standard graph of Lamivudine showed good linearity with R2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

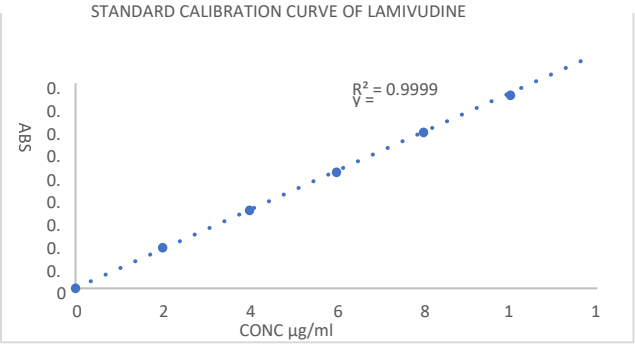


Figure 2: standard calibration curve of lamivudine

FTIR

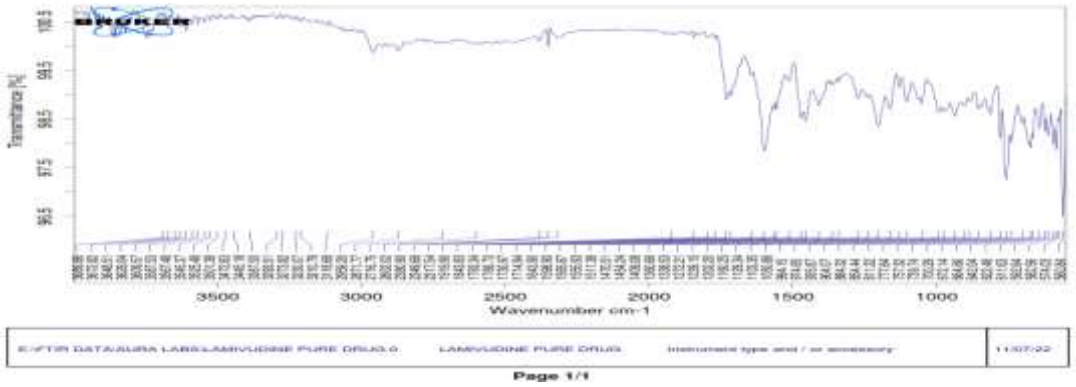


Figure 3: Lamivudine Pure drug FTIR

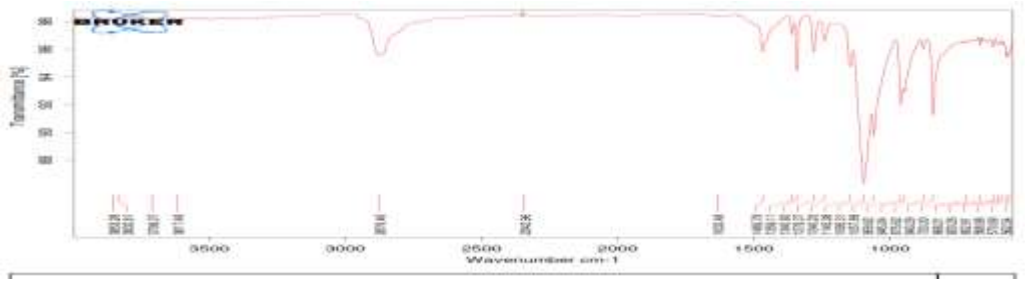


Figure 4: FTIR of drug +excipients

Infrared studies were carried out to confirm the compatibility between the lipid, drug, and selected excipients. From the spectra it was observed that there was no major shifting, as well as, no loss of functional peaks between the spectra of the drug and transfersomes gel. This indicated no interaction between the drug and other excipients

CHARACTERISATION OF PREPARED LAMIVUDINE TRANSFEROSOMES

Particle Size of Prepared Lamivudine Transfersomes F3 showed the least partice size of 98.19±18.50 nm

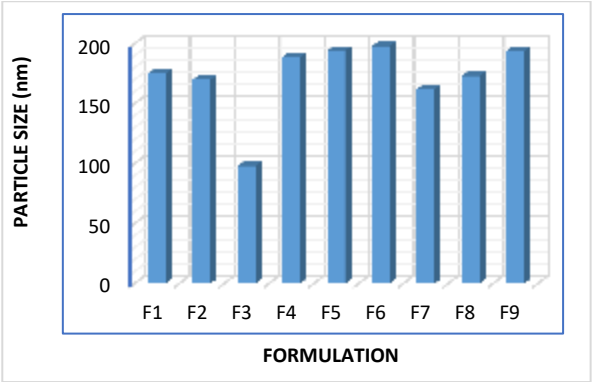


Figure 5: Particles size graph of Lamivudine Transfersomes (All Formulation)

ZETA POTENTIAL AND PDI

Table 7: Zeta potential and PDI of all formulation

FORMULATION	Zeta Potential	PDI
F1	-34.04±2.27	0.342
F2	-42.92±1.35	0.321
F3	-55.62±3.65	0.102
F4	-26.88±1.45	0.421
F5	-31.23±4.61	0.481
F6	-37.01±2.72	0.491
F7	-24.89±1.16	0.381
F8	-35.18±3.57	0.331
F9	-41.66±1.42	0.492

SD±(n=3)

F3 formulation highest zeta potential and it had good stability.

As shown in the table PDI of F3 formulaion is least when compared to other formulation

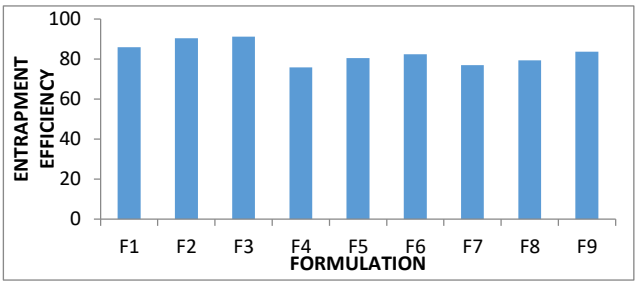


Figure 6: Entrapment efficiency graph of Lamivudine Transfersomes F3 showed highest 91.17±3.84

***IN-VITRO* DIFFUSION STUDIES**

Table 8: *In vitro* diffusion studies of F1-F9 Transfersomes formulations in percentage

TIME	CUMULATIVE PERCENT DRUG RELEASE								
H	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	10.26±0.11	16.83±0.23	20.31±0.67	21.60±0.87	25.43±2.1	09.91±0.5	16.12±0.8	20.52±0.8	18.75±0.7
2	18.80±0.32	20.95±0.34	26.14±0.56	26.94±0.67	29.82±3.4	16.58±0.5	20.90±0.8	26.33±0.6	21.63±0.7
3	22.96±0.44	31.61±0.54	32.67±0.78	36.56±0.67	34.97±2.3	24.82±0.7	36.56±0.5	31.98±0.8	26.98±0.8
4	29.57±0.32	36.15±0.65	46.52±0.89	43.13±0.87	38.69±5.3	31.94±0.8	42.35±0.8	38.36±0.6	32.76±0.6
5	33.34±0.45	45.75±0.43	51.74±0.98	48.75±0.78	46.28±4.5	36.56±0.7	56.92±0.8	42.61±0.9	40.12±0.5
6	47.21±0.71	48.56±0.65	68.61±0.45	54.82±0.76	50.15±1.2	42.71±0.7	63.84±0.7	47.18±0.9	46.34±0.4
7	54.93±0.23	56.90±0.56	73.96±0.45	61.34±0.87	57.67±3.4	48.38±0.9	72.27±0.5	55.15±0.4	53.18±0.3
8	60.76±0.56	61.38±0.56	77.81±0.87	68.95±0.10	63.75±0.1	62.17±0.9	77.16±0.5	62.22±0.5	57.65±0.6
9	66.83±0.32	68.19±0.78	88.18±0.98	72.26± 1.2	69.41±0.3	67.49±0.8	85.26±0.5	67.64±0.4	61.21±0.5
10	76.54±0.24	75.21±0.78	96.42±0.32	79.15±1.7	75.25±0.5	72.24±0,6	80.33±0.4	76.63±0.4	89.17±0.4

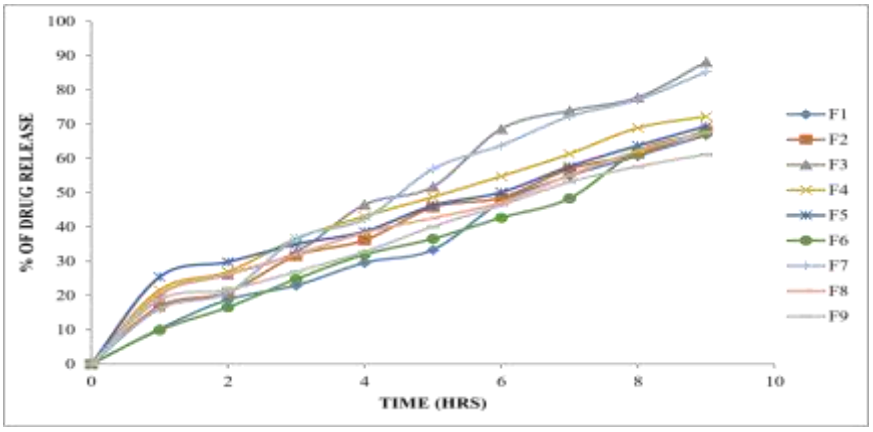


Figure 7: *In vitro* diffusion studies of F1-F9 Transfersomes formulations in percentage

CHARACTERISATION OF OPTIMIZED FORMULATION

Surface morphology of optimized formulation

The transfersomes were subjected to microscopic examination (S.E.M) for characterizing size and shape of the transfersomes. Microscopic examination revealed, spherical small uni-lamellar vesicles size.

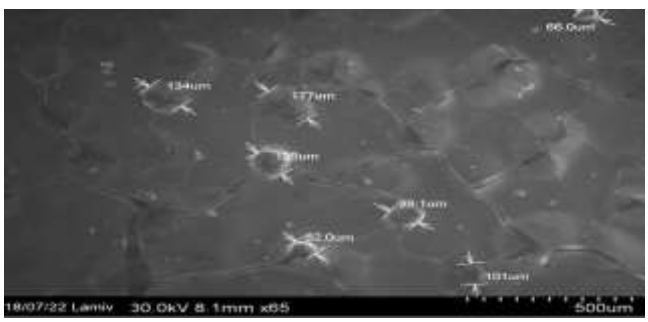


Figure 8: SEM Photograph of Lamivudine Transfersomes (Formulation-3)

PARTICLE SIZE

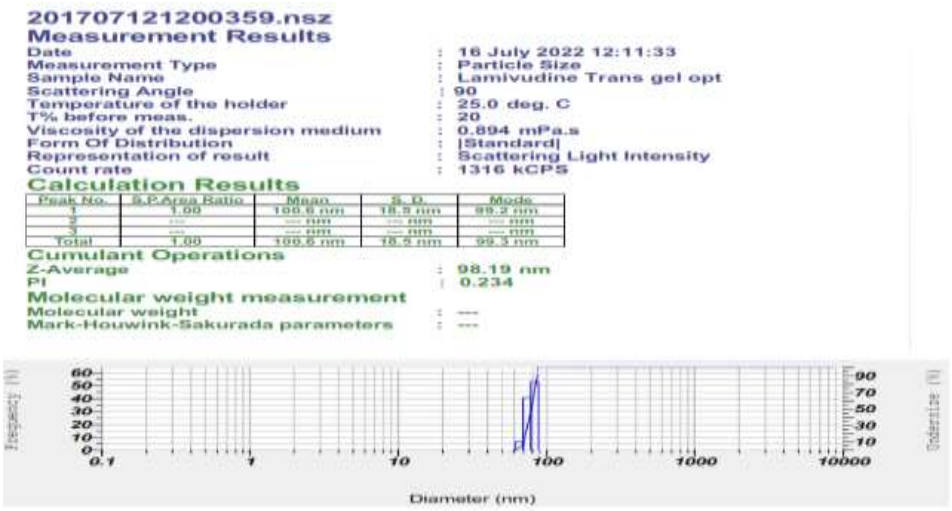


Figure 9: Particle size of F3 Formulation

ZETA POTENTIAL

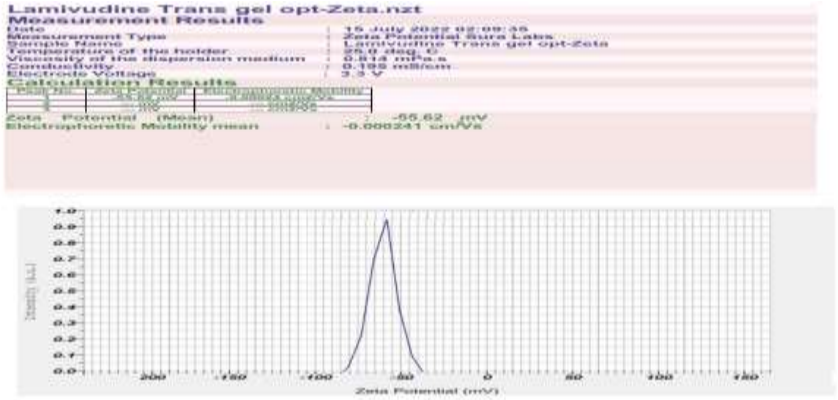


Figure 10: Zeta Potential of F3 Formulation

CHARACTERISATION OF GEL

Table 9: gel evaluation parameter of F3

Formulation F3 optimized Poloxamer 407 gel	pH	Viscosity (cps)	Extrud ability	Spread ability (Gm.cm/sec)	Homogeneity	Drug Content	Skin Irritation test
0.5%	5.64	5154	+	6.56	Satisfactory	93.19	No
1%	5.16	5597	+	6.27	Satisfactory	96.02	No
2%	5.01	5960	++	6.01	Excellent	97.29	No

Table 10: *In-vitro* diffusion studies of Transfersomes gel:

Time (hrs)	F3 optimized 0.5% Poloxamer gel	F3 optimized 1% Poloxamer gel	F3 optimized 2% Poloxamer gel
0	0	0	0
1	48.96	35.72	29.30
2	59.31	49.01	34.62
4	67.24	52.82	42.06
6	71.59	64.02	51.10
8	80.07	73.94	63.16
10	92.41	81.18	70.24
12		86.20	75.18
18		90.54	82.44
24			97.31

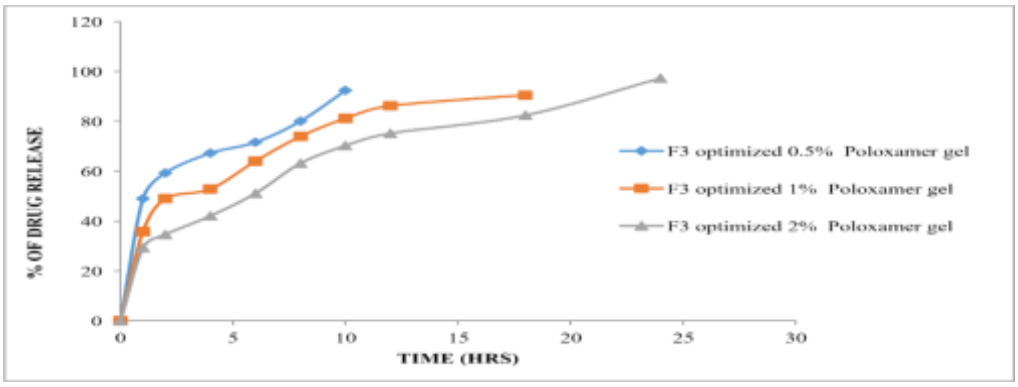


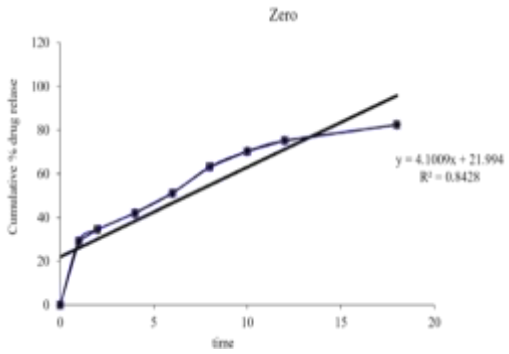
Figure 11: *invitro* diffusion studies for Transfersome gel with different concentrations of Poloxamer.

F3 optimized 2% Poloxamer gel highest drug release (97.31% for 24 hours), good Homogenity, highest drug content, Proper viscosity. Hence it was considered as optimized formulation.

KINETIC STUDIES

Table no.11: Release kinetics of optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
29.3	1	1.000	1.467	0.000	1.849	29.300	0.0341	-0.533	70.7	4.642	4.135	0.507
34.62	2	1.414	1.539	0.301	1.815	17.310	0.0289	-0.461	65.38	4.642	4.029	0.613
42.06	4	2.000	1.624	0.602	1.763	10.515	0.0238	-0.376	57.94	4.642	3.870	0.772
51.1	6	2.449	1.708	0.778	1.689	8.517	0.0196	-0.292	48.9	4.642	3.657	0.985
63.16	8	2.828	1.800	0.903	1.566	7.895	0.0158	-0.200	36.84	4.642	3.327	1.314
70.24	10	3.162	1.847	1.000	1.474	7.024	0.0142	-0.153	29.76	4.642	3.099	1.543
75.18	12	3.464	1.876	1.079	1.395	6.265	0.0133	-0.124	24.82	4.642	2.917	1.725
82.44	18	4.243	1.916	1.255	1.245	4.580	0.0121	-0.084	17.56	4.642	2.599	2.042
97.31	24	4.899	1.988	1.380	0.430	4.055	0.0103	-0.012	2.69	4.642	1.391	3.251



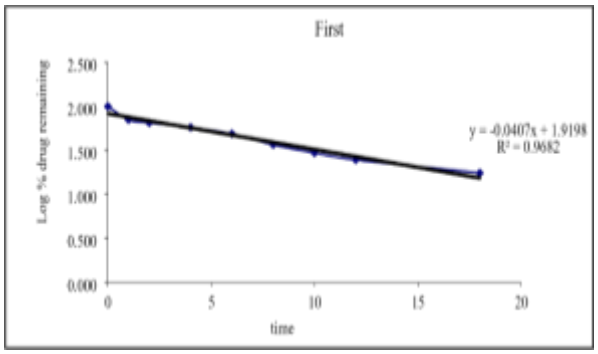
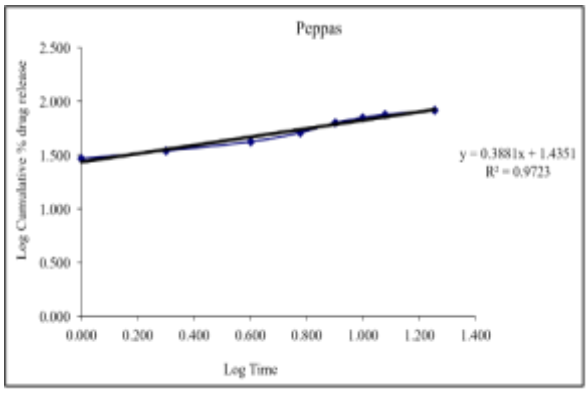


Figure12: Zero order release kinetics **Figure 13: First order release kinetics**



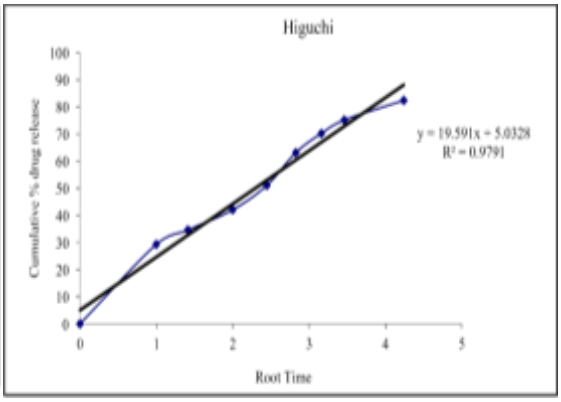


Figure 14: peppas and higuchi release kinetics

The optimised formulation F3 optimised 2% Poloxamer 407 Transfersomes gel was analyzed for the drug release mechanism. The best correlation coefficient value (0.979) indicates the best release mechanism (Higuchi release kinetics).

STABILITY STUDIES

Table 12: Stability studies of 2%Transferosomal gel at refrigerated and at room temperature

Time of storage in days	Temperature of storage			
	(Room temperature)		($4^0C \pm 2^0C$(Refrigerator temperature)	
	Drug content (%)	Entrapment efficiency (%)	Drug content (%)	Entrapment efficiency (%)
0	91.85±0.67	93.71±0.72	93.95±0.67	93.73±0.98
30	90.89±0.43	92.72±0.91	93.75±0.79	91.51±0.12
60	90.61±0.12	91.80±0.62	91.18±0.67	89.52±0.74
90	88.69±0.21	90.95±0.67	90.40±0.33	89.50±0.32

The values are expressed as mean, ± SD(n=3)

Stability studies were performed as per the conditions given in ICH guidelines for climatic zone IV Table 12 shows stability studies showed that Transferosomal gel is more stable at 4˚C when compared to other temperatures

CONCLUSION

The aim of the study was to formulate and evaluate Transferosomal gel of lamivudine. Preformulation studies shows high solubility of lamivudine in phosphate buffer pH 6.8 and FTIR shows no interaction between drug and excipients, Absorption maxima of lamivudine in methanol was found to be 270 nm. Total nine formulations were formulated and optimised formulation F3 showed entrapment efficiency EE (91.17), %CDR (96.12) and small particle size (98.19 nm). SEM of optimized lamivudine Transferosomes appeared as spherical, well identified, unilamellar nanovesicles. The optimized formulation of Transferosomes was further formulated to gel with Poloxamer 407 gel 0.5%,1% and 2% w/w, HPMC k15, Propylene glycol, DMSO. Among these F3 formulation with Poloxamer 407 2%w/w transferosomal gel is the optimised transferosmal gel and showed Spreadability value 6.01±0.12 cm, pH value 5.01 ±0.47. The actual drug content of the Transferosomal gel was found to be 97.29 ±0.66%, which represents good content uniformity. The viscosity of lamivudine Transferosomal gel is found to 5960 ±0.75cps. The percentage drug release for lamivudine Transferosomal gel is 97.31 %. stability studies showed that Transferosomal gel is more stable at 4˚C when compared to other temperatures.The percentage drug release for lamivudine Transferosomal gel is 97.31 %. stability studies showed that Transferosomal gel is more stable at 4˚C when compared to other temperatures.

CONFLICTS OF INTEREST: The authors have no conflicts of interest regarding this investigation .

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