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Formulation and Evaluation of Gentamicin-Loaded Transferosomal Gel

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ABSTRACT

Gentamicin is a broad-spectrum antibiotic that is utilized in treating infections caused by strains of Streptococci, Staphylococci, Pseudomonas, and gram-negative bacteria. Gentamicin, being a BCS class III drug possess poor permeability. The aim of the current research was to formulate and optimize Gentamicin-loaded topical transferosomal gel to enhance its permeability. The components such as, surfactants, edge activators, phospholipids were screened individually with drug. The transferosomal gel formulations were prepared by thin film hydration method. The formulations had particle size ranging from (113.98±2.51 nm) to (309.09±1.10nm), in vitro drug release ranging from (75.98±0.55%) to (97.13±0.24%), Zeta potential(-34.56mV) to (-13.18mV), PDI ranging from (0.205) to (0.542). The Optimization of Transferosomal gel was done on the basis of different concentrations of Carbopol 934 and HPMC k15 and the optimized formulation is characterized for viscosity, spreadability, SEM analysis, pH, drug content and in vitro drug release. The 0.1 % Gentamicin transferosomal gel had Spreadability 0.301±0.25 g.cm/sec, pH value is 6.1. Viscosity of optimized Gentamicin transferosomal gel was found to be 68521cps, and percentage drug release for was 98.59 ± 0.46. Finally, stability studies were carried out for prepared transferosomal gel and it was stable at30°C ± 2°C / 65 % ± 5 % RH for 90days.

Keywords: Gentamicin Transferosomal gel, Transferosomes, Topical, Antibiotic drug, Thin Film Hydration Technique.

1. INTRODUCTION:

Transdermal treatment systems are characterized as self-containing and discrete dosage types, which supply the medication with a regulated rate of systemic circulation through the skin when applied to the intact skin.[1] The medication system provides a range of potential benefits over traditional routes, such as the prevention of first-pass metabolism, predictable and extended activity, short-term use of medicines, improved physiological or drug responses, a reduction in negative side-effects, avoided fluctuations in drugs levels, inter-patient and intra-patient variations and, most importantly, minimized adverse effects.[2] A major obstacle to dermal and transdermal drug delivery is the permeation characteristics of the stratum corneum, which limits drug transport, making this route of administration frequently insufficient for medical use. Stratum corneum is the top layer of the epidermis consists of keratinized, flattened remnants of once actively dividing epidermal cells, impermeable to water and behaves as a tough flexible membrane. Many novel drug delivery systems have been investigated to evade this barrier.[3] A variety of methods in the field of medical research have been used to improve the effectiveness of material across to intact skin using

penetrators, enhancers, ionotophoresis, sonophoresis and vesicular constructions. The word "vesicular constructs" is used with liposomes, niosomes, virosomes, ethosomes and
transfersomes.[4] Vesicular drug delivery systems (VDDSs) are favorable over conventional dosage forms due to the fact that both lipophilic and hydrophilic drugs can be entrapped in the bilayer, respectively in the aqueous core.[5] Furthermore, these vesicular formulations had been more exploited in the field of transdermal drug delivery.[6] They offer many advantages over conventional delivery systems like biocompatibility, non-toxicity, and ability to modify drugs' bioavailability.[7] Transferosomes are ultra-flexible vesicles with a bilayer structure. They can penetrate the skin easily and overcome the barrier function by squeezing through the intracellular lipid of the stratum corneum.[8] Transfersomes are considered advantageous in topical and systemic drug delivery for the following distinctive features. On the one hand, transfersomes offer a great encapsulation efficacy up to 90% of drugs with a low or high molecular weight and a large variety in solubility. Moreover, the API is protected from biodegradation and a laggard, incrementally drug release is enabled due to depot function. Regarding production, an easy expansion to large-scale is possible. Despite these benefits, transfersomes still suffer from some shortcomings such as tendency of oxidative degradation, a range in purity of phospholipids from natural origin and an expensive production.[9 , 10] Transferosomes majorly involve the ingredients like amphipathic ingredients (combination of hydrophilic and lipophilic molecules like soy phosphatidylcholine), surface activators (e.g., surfactants), alcohol, and water. Apart from phospholipids, edge activators such as tween 80 or span 60 are the main constituents in the formulation of transfersomes. This single chain surfactants effect the destabilization of the lipid bilayers leading to an increase in its malleability making them particularly suitable for skin penetration.[11,12] The combination of the transferosomal suspension with the gel matrix can lead to formulation of a transferosomal gel, which may prove to be more pertinent for transdermal drug delivery.[13] Gentamicin is a broad-spectrum amino glycoside type antibiotic that is isolated from Micromonispora purpurea. Gentamicin kills bacteria by damaging the plasma membrane and binding to the 16s ribosomal RNA, leading to the inhibition of microbial protein synthesis. It is effective against wide spectrum of gram positive and gram-negative bacteria.[14] This study is designed to incorporate Gentamicin in the transferosomal gel system for transdermal delivery to avoid problems related with its parenteral delivery, and to improve the drug permeation through the skin and finally increase the bioavailability.

2. MATERIAL AND METHODS:

2.1 collection of drug and excipients

Gentamicin (Provided by Sura Labs), Carbopol 934, HPMC K15, Propylene Glycol are purchased from Merck Limited, Mumbai (India), Methyl Paraben , Soya-phosphatidylcholine ,Span 80 Purchased from SD Fine- Chem Limited, Mumbai.

2.2 Preformulation studies:

Organoleptic properties:

A small quantity of sample is taken and spread evenly on the white paper and examined visually for color, odour and texture.

Solubility:

To study the solubility of Gentamicin, excess quantities of the drug were added to 10 mL of different solvents. These flasks were kept for shaking in an orbital shaker at room temperature. Samples were collected at specified time intervals and filtered using filter paper (Whatman), followed by dilution with respective solvent. Then the concentration was analyzed by UV spectroscopy.

Melting point:
The melting point of Gentamicin was determined by capillary tube method according to the USP. A sufficient quantity of Gentamicin powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Gentamicin in the tube passed into liquid phase.

Determination of absorption maxima:
A solution containing the concentration 10 µg/ ml drug was prepared in 6.8 phosphate buffer, UV spectrum was taken using Lab India Double beam UV/VIS spectrophotometer (Lab India UV 3000+). The solution was scanned in the range of 200 – 400 nm.

Calibration curve of Gentamicin:
100 mg of Gentamicin was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL). 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 5, 10, 15, 20 and 25 µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}).

Drug – excipient compatibility study:
FTIR
The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients FT IR analysis of the pure drug was carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY), by K-Br pellet method. The samples were analyzed between wave numbers 4000 and 400 cm-1

FORMULATION AND DEVELOPMENT

Formulation development Gentamicin loaded transferosomes-thin film hydration technique:
Soya-phosphatidylcholine, Surfactant (Span 80/ Tween 80) with different molar ratios and Gentamicin sulphate (40mg) were dissolved in alcohol. Then solution was put in a round bottom flask. These were then dissolved by shaking., using rotary evaporator, thin lipid film on the internal surface of the round-bottomed flask was formed, at 40ºC. Then prepared thin film is kept under vacuum for 12 hrs to remove final traces of solvent, after which it is hydrated with buffer (pH 6.5) at 60 rpm for 1 hour at room temperature, to form large multilamellar vesicles, the resulting suspension was sonicated for 30 min using probe sonicator at 380 W, and then homogenized using polycarbonate membranes, to form smaller vesicles.

Table 1: Formulation code for preparation of transferosomes

S.No.	Formulation code		PC:S (mg)	Drug (mg)
1	F1	Span 80	100:50	40
2	F2	Span 80	150:50	40
3	F3	Span 80	100:25	40
4	F4	Tween 80	100:50	40
5	F5	Tween 80	150:50	40
6	F6	Tween 80	100:25	40

S=Surfactant, PC=Phosphatidylcholine

Preparation of transferosomal gel of Gentamicin –
Optimization of Transferosomal gel was done on the basis of concentration of Carbopol 934 and HPMC k15 (0.5%, 0.1%, 1.5%, and 2%) as described in the table below. The polymer was dispersed in distilled water. Then the mixture was stirred until it gets thickened. After complete dispersion, propylene glycol was added slowly into the aqueous dispersion of polymer, and other ingredients, such as Methyl Paraben and triethanolamine were added. 10 ml of transfersomes dispersion was incorporated into polymer gel with continuous stirring. Quantity sufficient distilled water was added to make up the volume up to 100 gm of gel

Table 2: Formulation Chart of Topical Transfersome Gel Formulation:

Ingredients	FORMULATION							
Gentamicin optimized transferosomes	0.1 %	0.1 %	0.1 %	0.1 %	0.1%	0.1%	0.1%	0.1%
Carbopol 934	0.5%	1%	1.5%	2%	-	-	-	-
HPMC k15	-	-	-	-	0.5%	1%	1.5%	2%
Propylene Glycol	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%
Methyl Paraben	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%	0.03%
Triethanolamine	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

CHARACTERIZATION OF GENTAMICIN LOADED TRANSFEROSOMES

Vesicle morphology-

It can be determined using scanning electron microscopy

Particle Sizes, PDI, Zeta Potential:

The mean particle length and polydispersity index (PDI), that's a degree of the distribution of transfersomes, was decided the usage of dynamic light scattering (Delta Nano C, Beckman counter), and Zeta capability becomes anticipated on the premise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS (Malvern Instruments, UK).

Entrapment efficiency [15,16]

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 37oC 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 Gentamicin. The amount of Gentamicin 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:

All prepared gel formulations have been observed for their visual appearance, such as transparency, colour, texture, grittiness, greasiness, stickiness, smoothness, stiffness and tackiness. 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 particles or grittiness.

P^H of formulation:[17,18]

pH measurement of the gel was measured by using a digital pH meter (Lab India SAB 5000), dipping the glass electrode completely into the gel system, taken in a 10ml beaker. The observed pH values were recorded for all formulations (F1-F6).

Determination of viscosity

Viscosities of the gels were determined by using Brookfield Viscometer (model-RVTP). Spindle type, RV-7 at 100 rpm. 100gm of the gel was taken in a beaker and the spindle was dipped in it and rotated for about 5 minutes and then reading was taken.

Homogeneity:

The homogeneity of Gentamicin Transfersomal gels were checked by visual inspection. In this regard the gels were filled into narrow transparent glass tubes and were checked in light for the presence of any particulate or lump.

Spreadability: [18,19]

For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1kg weight for

5 min. weight (50 g) was added to the pan. The time in which the upper glass slide moves over to the lower plate was taken as measure of spread ability.

S = M.L / T

M- Weight tied to the upper slide
L - Length moved on the glass.
T - Time Taken

Fourier Transform Infrared (FTIR) spectroscopy:

FT IR analysis of the pure drug and optimized formulation were carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY).

***In-vitro* diffusion study** [19]

An in-vitro drug release study was performed using modified franz diffusion cell. Dialysis membrane, was placed between receptor and donor compartments. transferosomal gel 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 205 nm using phosphate buffer pH 6.8 as blank.

Surface Morphology

Sample was examined by using SEM **(**Scanning Electron microscope) (Hitachi, Japan).

Drug content [20]

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 205 nm. drug content was calculated by linear regression analysis of the calibration curve.

Stability studies

The stability study of the Transfersomal gels was performed as per ICH guidelines. Freshly prepared formulations were divided into groups and kept at specified storage conditions as per ICH guidelines. The sample was withdrawn periodically and tested for various evaluation parameters**.**

4. RESULTS AND DISCUSSION

4.1 Preformulation Studies:

a. Organoleptic properties

Table 3: Organoleptic Properties of Gentamicin

S NO.	Properties	Observed Results
1	State	Solid
2	Colour	White
3	Odor	Odorless
4	Appearance	Amorphous Powder

b. Melting point determination:

Table 4: Melting point determination of Gentamicin

S. No	M.P	Literature Value [21]
1.	220°C	218°C-237°C

Observation: the melting point of gentamicin was observed to be 220ºC. indicating the purity of drug sample.

c. Solubility results

Table 5: solubility of Gentamicin

S no.	Solvents	Concentration [µg/ml]
1	Water	63.15 ± 0.58µg/ml of drug
2	Methanol	45.08 ± 0.51 µg/ml of drug
3	pH 6.8 Phosphate Buffer	54.15 ± 0.58 µg/ml of drug
4	Dimethyl formamide	37.25 ±0.52 µg/ml of drug
5	Ethanol	29.46 ± 0.57 µg/ml of drug
6	Acetonitrile	23.38 ± 0.56 µg/ml of drug

Observation: Gentamicin was found to be soluble in methanol and phosphate buffer(6.8pH) and soluble in water, ethanol, Acetonitrile, Dimethyl Formamide.

4.2 UV-Spectroscopy-Analysis of Drug

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

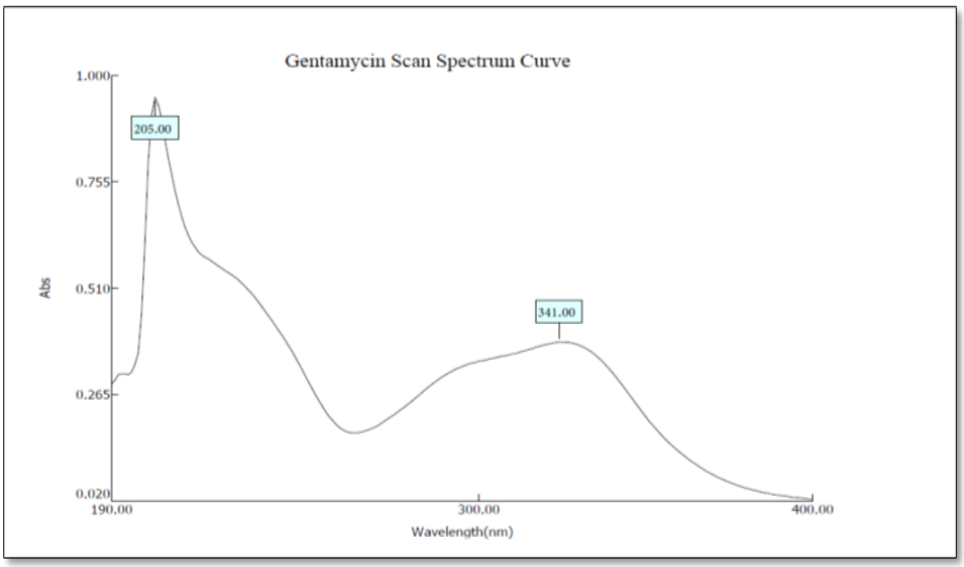

Figure 1: Lamda max determination of Gentamicin

Gentamicin solution of 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 205 nm, therefore , it was selected as the wavelength for detection in phosphate buffer pH6.8

e. Calibration curve:

The standard graph of Gentamicin showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law

Table 6: Calibration curve data of Gentamicin in phosphate buffer pH 6.8.

Concentration (µg/ml)	Absorbance (at 205 nm)
0	0
5	0.114 ± 0.197
10	0.234 ±0.312
15	0.354 ±0.419
20	0.471 ±0.543
25	0.587 ±0.510

SD±(n=3)

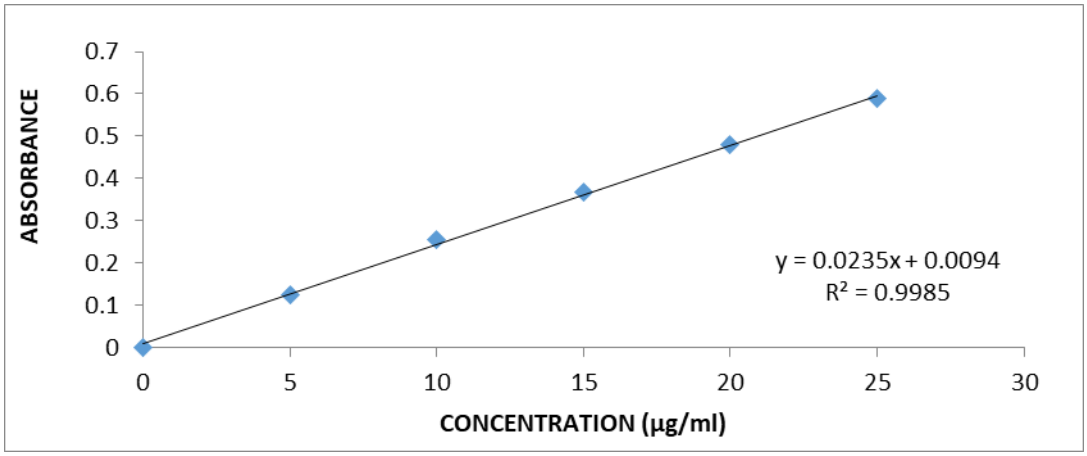

Figure 2: Standard calibration curve of Gentamicin

FTIR

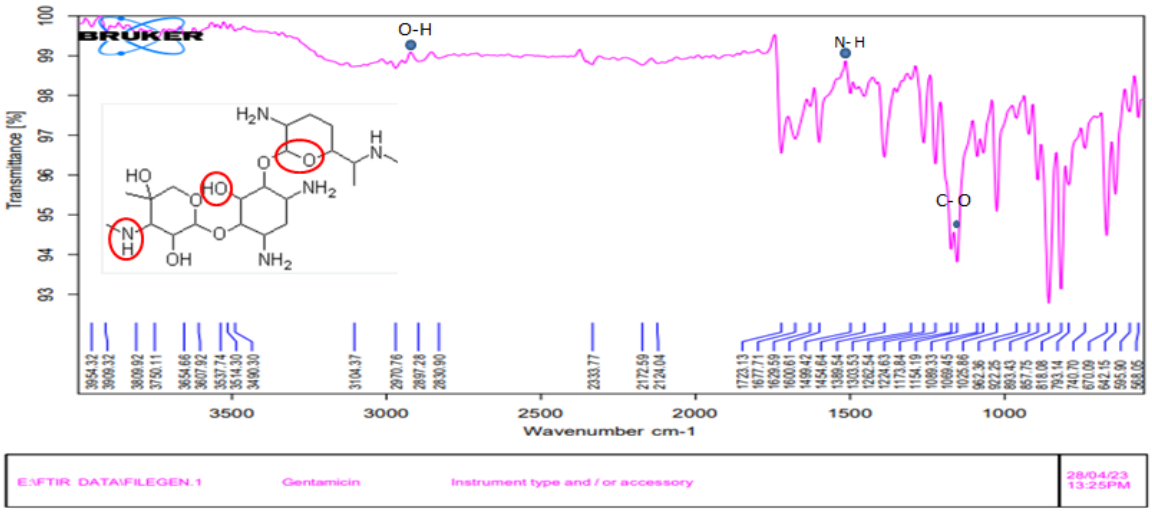

Figure 3: FTIR of Gentamicin Pure drug

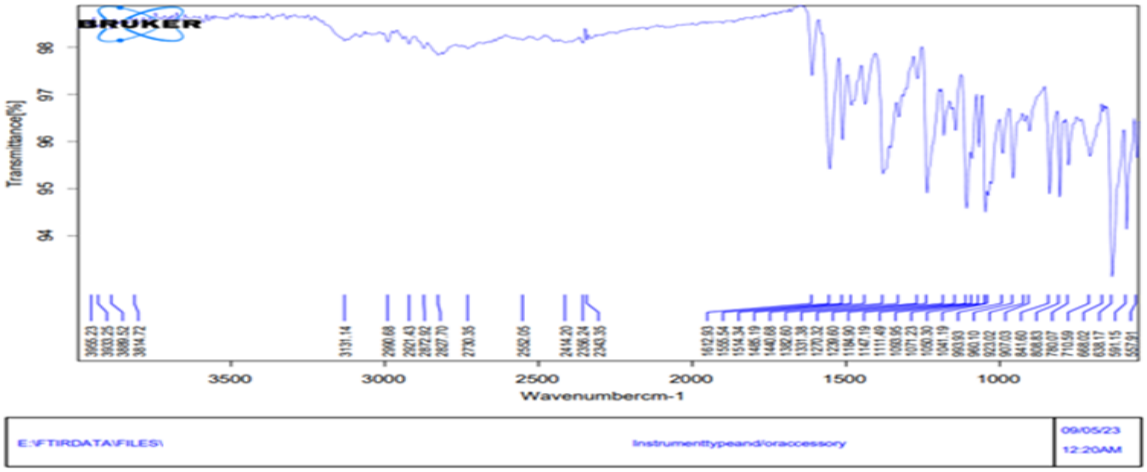

Figure 4: FTIR of drug +excipients

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 GENTAMICIN TRANSFEROSOMES

Table 7: Particle Size, PDI, Zeta potential, Entrapment Eficiency, and Drug Content of all formulations

Formulation	Particle sizes (nm)	PDI	Zeta potential (mV)	Entrapment efficiency (%)	Drug content (%)
F1	171.31±2.11	0.542	-15.61	76.43±1.50	89.25±0.08
F2	215.19±2.25	0.309	-18.93	70.30±0.21	82.15±2.10
F3	113.98±2.51	0.205	-34.56	89.18±2.20	97.65±2.09
F4	157.87±4.13	0.481	-13.18	74.90±1.42	86.14±3.40
F5	309.09±1.10	0.360	-20.24	80.53±1.03	90.75±0.30
F6	272.10±2.32	0.326	-23.83	81.09±2.12	93.69±3.18

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

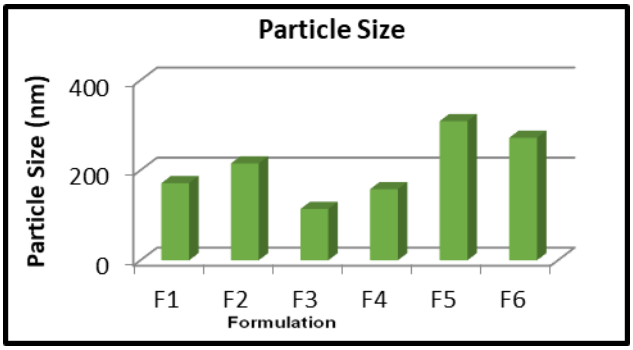

Figure 5: Particles size graph of Gentamicin Transfersomes (All Formulation)

Particle Size of Prepared Gentamicin Transfersomes F3- formulation showed the least partice size of 113.98±2.51 nm

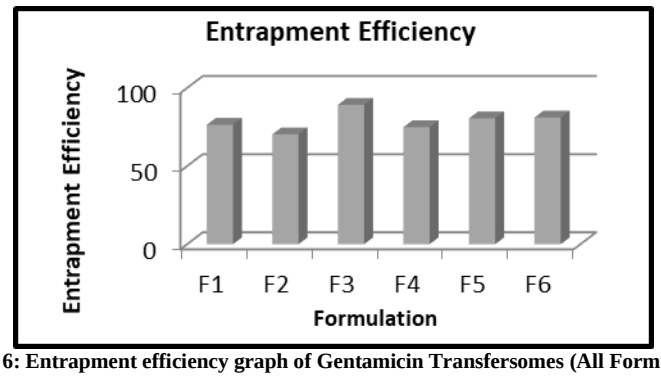

Figure 6: Entrapment efficiency graph of Gentamicin Transfersomes (All Formulation)

Transfersomes F3- formulation showed highest entrapment efficiency 89.18±2.20 %

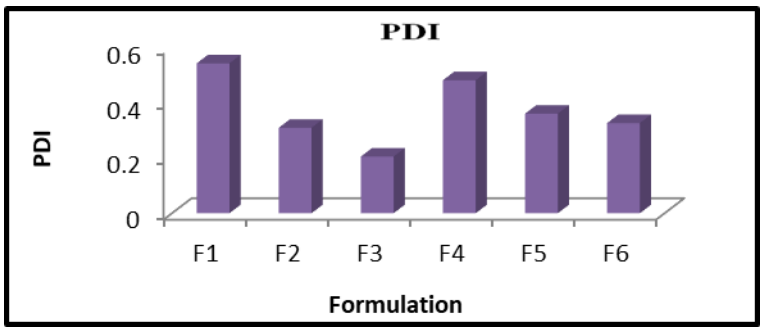

Figure 7: PDI graph of Gentamicin Transfersomes (All Formulation)

IN-VITRO DIFFUSION STUDIES

Table 8: *In vitro* diffusion studies of F1-F6 Transfersomes formulations in percentage release

Time (hour)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	25.42±0.75	36.14±0.89	48.14±2.13	41.15±0.65	38.45±0.11	31.18±0.30
2	32.37±0.50	43.01±0.17	59.77±0.23	50.89±0.54	45.18±0.30	38.99±0.24
4	39.14±0.23	52.33±0.24	65.91±0.53	56.50±0.97	49.25±1.62	44.01±0.86
6	47.96±0.32	56.12±0.33	70.52±0.45	67.19±0.34	55.87±0.95	51.55±0.15
8	56.69±0.69	64.75±0.41	75.17±0.68	70.56±0.76	59.93±0.57	57.31±0.44
10	59.75±0.75	71.41±0.54	78.28±0.22	76.24±0.54	63.21±0.38	62.78±0.41
12	64.27±0.88	78.22±1.22	82.35±0.13	80.11±0.34	68.58±0.49	65.47±0.37
18	70.33±0.24	82.08±1.43	93.11±0.09	85.80±1.87	72.12±0.91	70.16±0.18
24	75.98±0.55	93.17±1.69	97.13±0.24	90.02±1.36	85.75±0.66	79.50±0.66

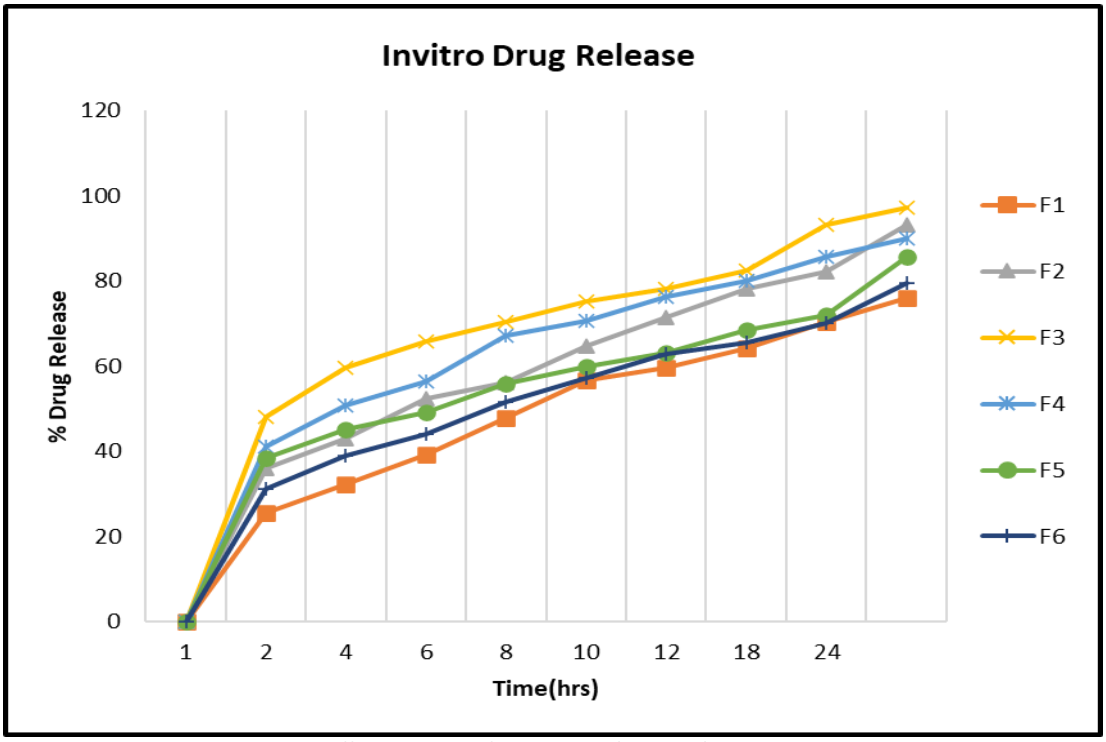

Figure 8: *In vitro* diffusion studies of F1-F6 Transfersomes formulations in percentage

In vitro drug release study of the selected Transfersomes (F1, F2, F3, F4, F5 and F6) was carried out. The Transfersomes exhibited 24 hours sustained release pattern. Fifty percent of the incorporated number of drugs was found to be released during the first 2 hours, followed by a slowed release of 97.13% of the drug up to 24 hours. The Gentamicin Transfersomes F3 showed a better release profile of 97.13 % by 24 hours. The prolonged release at 24 hours can be attributed to slow diffusion of drug from lipid matrix.

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.

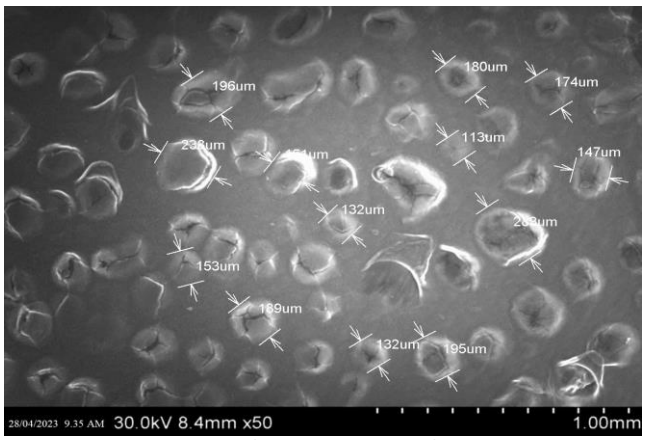

Figure 9: SEM Photograph of Gentamicin Transfersomes (Formulation-3)

PARTICLE SIZE

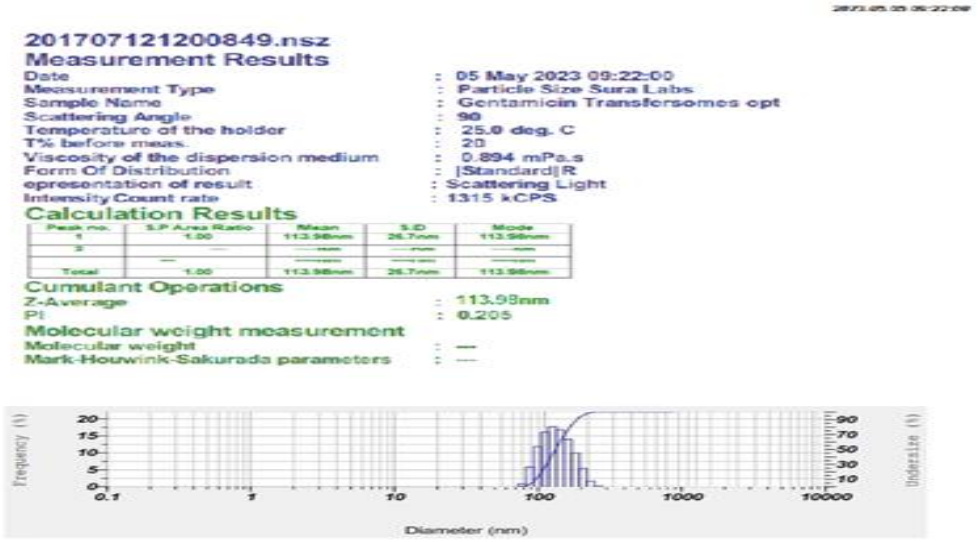

Figure 10: Particle size of F3 Formulation

ZETA POTENTIAL

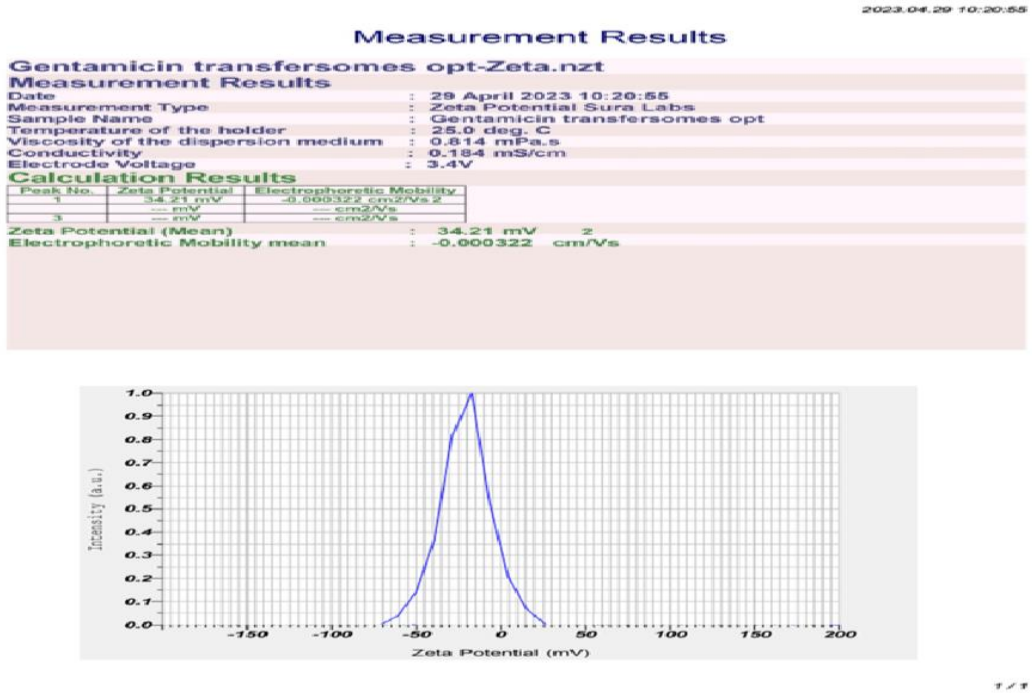

Figure 11: Zeta Potential of F3 Formulation

CHARACTERISATION OF GEL

Table 9: gel evaluation parameter of F3

Polymer	Formulation	pH	Viscosity (cp)	Extrudability	Homogeneity	Drug Content (%)
Carbopol	F3 optimized 0.5 %	6.4	62012	+	Satisfactory	90.14
	F3 optimized 1%	6.2	63158	+	Satisfactory	92.48
	F3 optimized 1.5%	6.1	68521	++	Satisfactory	97.88
	F3 optimized 2 %	5.8	69959	+	Satisfactory	95.20
HPMC k15	F3 optimized 0.5 %	6.2	58314	+	Satisfactory	86.18
	F3 optimized 1%	6.3	60147	+	Satisfactory	90.87
	F3 optimized 1.5%	6.5	62369	+	Satisfactory	93.54
	F3 optimized 2 %	6.4	64397	+	Satisfactory	94.30

Table 10: Colour , Spreadability of Transfersomes gel:

Polymer	Formulation	Colour	Spreadability (g.cm/sec)
Carbopol	F3 optimized 0.5 %	White to off white	0.512±0.81
	F3 optimized 1%	White to off white	0.382±0.15
	F3 optimized 1.5%	White to off white	0.301±0.25
	F3 optimized 2 %	White to off white	0.269±0.18
HPMC k15	F3 optimized 0.5 %	White to off white	0.615±0.62
	F3 optimized 1%	White to off white	0.523±0.20
	F3 optimized 1.5%	White to off white	0.510±0.16
	F3 optimized 2 %	White to off white	0.451±0.25

Table 11: *In-vitro* diffusion studies of Transfersomes gel:

Polymer	Carbopol				HPMC k15			
Time (hrs)	F3 optimized 0.5 %	F3 optimized 1%	F3 optimized 1.5%	F3 optimized 2%	F3 optimized 0.5 %	F3 optimized 1%	F3 optimized 1.5%	F3 optimized 2%
0	0	0	0	0	0	0	0	0
1	37.20±0.70	30.69±0.24	28.86±0.75	25.79±0.19	40.45±0.89	36.32±0.26	32.51±0.53	28.45±0.53
2	42.39±0.43	36.54±0.19	33.06±0.24	30.41±0.25	48.86±0.41	48.75±0.19	45.72±0.15	31.86±0.48
4	59.14±1.99	44.52±0.34	41.50±0.61	38.62±0.44	60.75±0.61	53.50±0.92	50.63±0.96	43.52±0.14
6	65.02±0.18	51.71±0.78	50.19±0.68	44.43±0.38	71.24±0.89	60.76±0.45	64.98±0.24	49.98±0.99
8	73.19±0.58	68.99±1.46	63.78±0.42	50.99±0.54	85.80±0.63	66.83±0.86	69.71±0.48	56.10±0.55
10	80.75±0.21	72.63±0.29	70.24±0.85	56.70±0.17	90.34±0.71	73.24±0.40	76.83±0.52	60.56±0.82
12	87.92±0.69	80.74±0.55	84.93±0.94	62.36±0.42	92.18±0.74	86.97±0.64	82.30±0.59	67.29±0.69
18	87.92±0.69	89.19±0.34	91.82±0.51	80.54±0.96	92.18±0.74	91.24±0.81	88.17±0.62	72.16±0.83
24	87.92±0.69	89.19±0.34	98.59±0.46	92.14±0.23	92.18±0.74	93.39±0.41	92.46±0.79	86.98±0.65

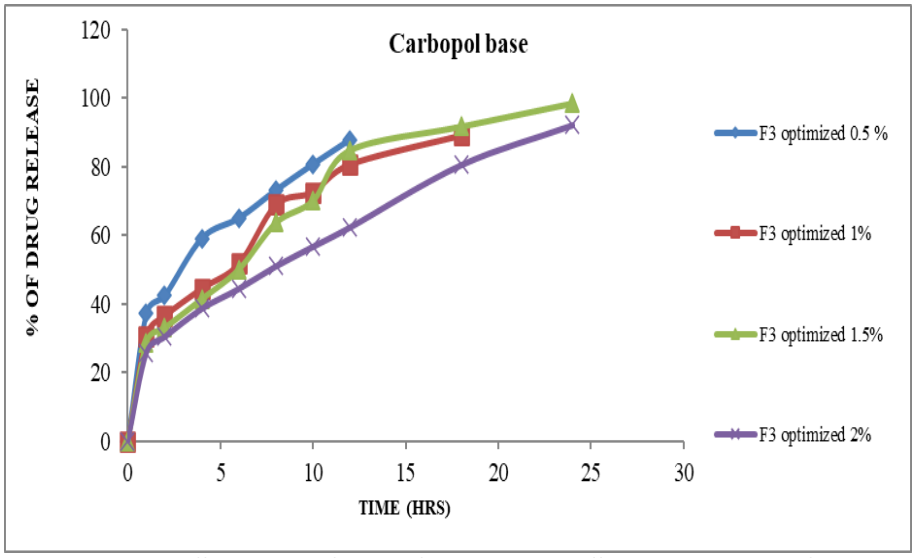

Figure 12: *invitro* diffusion studies for Transfersome gel with different concentrations of Carbopol

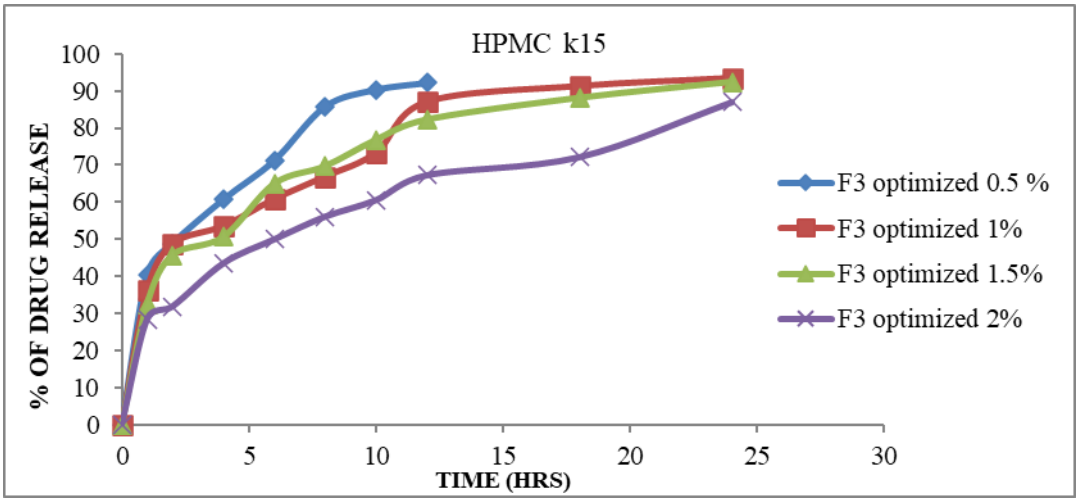

Figure 13: *invitro* diffusion studies for Transfersome gel with different concentrations of HPMC k15

F3 optimized 1.5% Carbopol gel highest drug release (98.59 % for 24 hours), good Homogenity, highest drug content, Proper viscosity. Hence it was considered as optimized formulation.

KINETIC STUDIES

Table no.12: Release kinetics of optimised formulation

Cumulative (%) release Q	Time (T) (hrs)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / t)	1/Cum % Release	PEPPAS log Q/100	% Drug Remaining	Q0 1/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
28.86	1	1.000	1.460	0.000	1.852	28.860	0.0347	-0.540	71.14	4.642	4.144	0.498
33.06	2	1.414	1.519	0.301	1.826	16.530	0.0302	-0.481	66.94	4.642	4.060	0.581
41.5	4	2.000	1.618	0.602	1.767	10.375	0.0241	-0.382	58.5	4.642	3.882	0.760
50.19	6	2.449	1.701	0.778	1.697	8.365	0.0199	-0.299	49.81	4.642	3.679	0.962
63.78	8	2.828	1.805	0.903	1.559	7.973	0.0157	-0.195	36.22	4.642	3.309	1.333
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
84.93	12	3.464	1.929	1.079	1.178	7.078	0.0118	-0.071	15.07	4.642	2.470	2.172
91.82	18	4.243	1.963	1.255	0.913	5.101	0.0109	-0.037	8.18	4.642	2.015	2.627
98.59	24	4.899	1.994	1.380	0.149	4.108	0.0101	-0.006	1.41	4.642	1.121	3.520

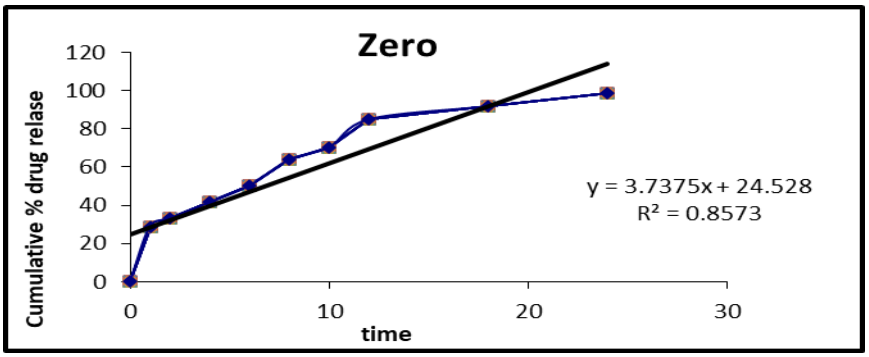

Figure14: Zero order release kinetics

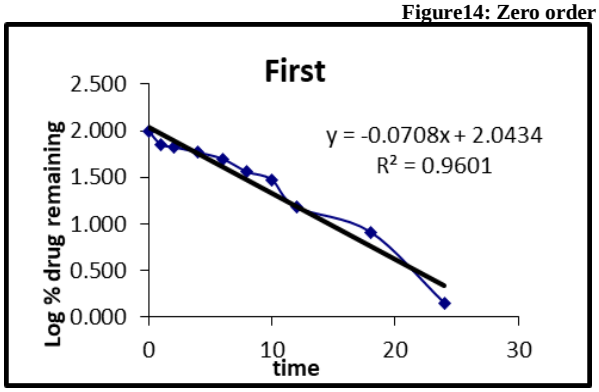

Figure 15: First order release kinetics

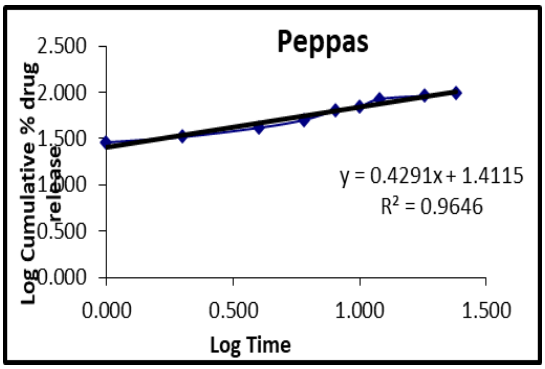

Figure 16: Peppas release kinetics

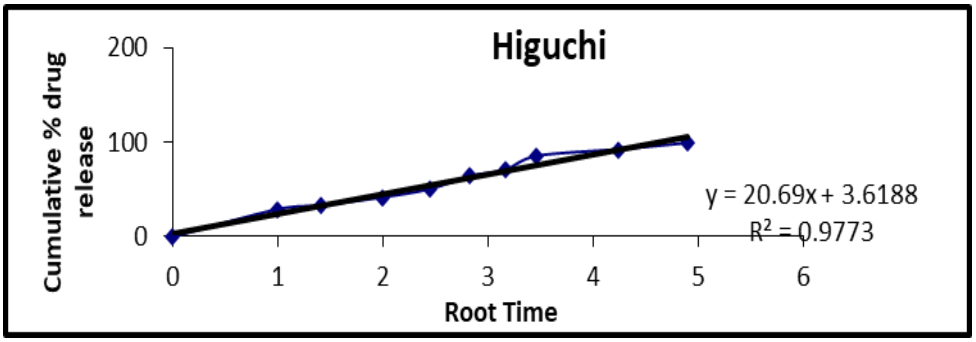

Figure 17: Higuchi release kinetics

The prepared F3 optimized 1.5 % Carbopol Transfersomes gels were subjected to the drug release kinetics and release mechanism. The formulations were studied by fitting the drug release time profile with the various equations such as Zero order, First order, Higuchi and Korsmeyer pappas The best correlation coefficient value (0.977) indicates **th*e best release mechanism (Higuchi).***

STABILITY STUDIES

Table 13: Stability studies of Transferosomal gel

Formulation	**F3**			
Storage Condition	30°C ± 2°C / 65 % RH ± 5 % RH			
Time interval (days)	0	30	60	90
Colour	White to off white	White to off white	White to off white	White to off white
Homogeneity	+++	+++	+++	+++
pH	6.1	6.0	6.0	5.9
Viscosity (cP)	67521	66018	64189	64095
Spreadability (g.cm/sec)	0.301±0.25	0.294±1.51	0.286±2.40	0.281±0.60
Extrudability	++	++	++	++
Drug content uniformity (%)	97.88	97.50	97.36	97.29
+++ Excellent, ++ Good, + Satisfactory, - Poor, -- Fail				

The stability study of the Transferosomal gels was performed as per ICH guidelines. Freshly prepared formulations were divided into groups and kept at specified storage conditions as per ICH guidelines. The sample was withdrawn periodically and tested for various evaluation parameters. There was not much more variation in the properties of transferosomal gel F3 under stability study as the formulation retained all the properties when stored at specified storage conditions over a while, indicating that the transferosomal gel was very much stable.

CONCLUSION

The aim of the study was to formulate and evaluate Gentamicin Sulphate loaded transferosomal gel. Pre-formulation research indicates excessive solubility of Gentamicin Sulphate in pH buffer 6.8 and FTIR indicates no interaction among drug and excipients, Absorption maxima of Gentamicin Sulphate in pH buffer 6.8 was observed to be 205 nm. Total 6 formulations have been prepared. It was observed that the optimized formulation was found to be F3 Formulation, which gave in-vitro dissolution of about of 97.13 % by 24 hours, entrapment efficiency EE, (89.17), and small particle size (113.98 nm). SEM of optimized gentamicin Transferosomes appeared as spherical, well identified, unilamellar vesicles.

The optimized formulation of Transferosomes was further formulated to gel with various concentrations of HPMC-K15, Carbapol 934. Among these F3 formulation with Carbapol 934 1.5%w/w transferosomal gel is the optimised transferosomal gel and showed Spreadability value 0.301±0.25 cm, pH value 6.1. The actual drug content of the Transferosomal gel was found to be 97.88

which represents good content uniformity. The viscosity of gentamicin Transferosomal gel is found to e 68521 cps. The percentage drug release for gentamicin Transferosomal gel is 98.59 % for 24 hours and drug release data of selected Transferosomal gel confirmed good fit into Higuchi release Kinetics. Stability studies showed there was not much more variation in the properties of transferosomal gel F3 under stability study as the formulation retained all the properties when stored at specified storage conditions over a while, indicating that the transferosomal gel was very much stable. Thus, formulated Gentamicin Sulphate loaded transferosomal gel represents to be efficient and stable for the transdermal delivery of an antibiotic drug like Gentamicin Sulphate.

Scope Of The Study:

Pharmacokinetic-Pharmacodynamic parameters to be evaluated, in addition.

Animal models- in vivo studies to be performed for prepared transdermal transferosomal gel

Long term stability testing is to be performed

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: The authors have no conflicts of interest regarding this investigation.

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