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DESIGN, DEVELOPMENT, AND IN VITRO EVALUATION OF CELECOXIB -LOADED TRANSFERSOMAL GEL

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Abstract:

The purpose of the present investigation was to design, development, and in vitro evaluation of celecoxib -loaded transfersomal gel Method: celecoxib -loaded transfersomal gel was prepared using Thin Film Hydration mechanism. Experiments using Fourier transform infrared spectroscopy and Differential Scanning Calorimetry were used to determine drug and excipients were compatible. 2^2 mathematical models have been employed for the optimization experiment in this work, which was carried out using Design Expert version 12 software. Vesicle size (Y1) and entrapment efficiency (Y2) are regarded as response variables or dependent factors, and the concentrations of lipids (in mg) and edge activators (in ml) are treated as independent factors. optimized formulation is having a high potential value i.e. - 32.1mV. High zeta potential value contributes to the stability of the formulation and the tendency to aggregate would be minimal. The Z average of the particle size for the improved formulation is discovered to be 249.2 nm and Transmission electron microscopy indicates the morphology of vesicles; the TEM pictures for CBT7 were found to be spherical with a uniform surface. The drug release percentage of CBT7 was 88.03 ±0.22 percent over 24 hours, following a regulated and predefined release pattern.

Key words: Transfersomal gel, Thin Film Hydration & by Fourier transform infrared spectroscopy.

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INTRODUCTION:

Transferosomes are the vesicular systems occluded with water in the core portion encircled by surfactants and lipids which are arranged in a bilayer. The lipophilic and ampiphilic drug is enfolded in the lipid bilayer by hydrophobic or electrostatic forces, the hydrophilic drug becomes stuck in the hydrophilic core[1-4].

Another name for transferosomes is a flexible or versatile vesicle. Gregor Cevc first proposed the idea of elastic vesicles in 1991. Since then, numerous studies have been conducted on these elastic vesicles using various names, such as "ectosomes" and "flexible vesicles." German company IDEAAG has registered the phrase "Transferosomes" as a trademark[5-8].

The name means "carrying body," which comes from the Latin word "transferee," which means to carry over, and the Greek word "soma," which means "for a body." The transporter A manufactured vesicle with properties resembling those of a natural cell vesicle, the transferosome is useful for the targeted and regulated release of medications.

One can refer to transferosomes as lipid droplets with exceptional flexibility, deformability, and stress receptivity. Through or from within the cells, transferosomes pierce the stratum corneum. When applied to the skin, these vesicular structures first investigate the hydrophilic pathways that are reachable via the skin and make use of them to enable the vesicles to enter together with the medication by transforming to complete the mission without compromising the integrity of the vesicles. Transferosomes' capacity to flex without losing their vascular integrity allowed them to effectively pass through various transport barriers..

MATERIALS AND METHODS:

Materials

Celecoxib was received from Granules India Limited, Hyderabad. Soya lecithin was purchased from Agro Solvent Products Ltd, Jayendra Ganj, Madhya Pradesh. Cholesterol were obtained from Invitrogen Bioservices India Pvt. Ltd, Bangalore.. Other chemicals used were of analytical grade.

Methods

Transferosomes Formulation Technique

Transferosomes were formulated by Thin Film Hydration mechanism. A clean and dry round bottomed flask was used to collect the required amounts of lipids Cholesterol and Soya lecithin in a 1:1 ratio, edge activator Span 80, and Pure drugs of Celecoxib. Add1:1 ratio of methanol and chloroform to the above composition. The resultant solution is subjected to rotary evaporation at room temp to 500c for 20 mins until the thin film is formed. The obtained thin film is hydrated using 5ml of Phosphate buffer in order to obtain the transferosomal suspension[9-12].

Optimization Process of Transferosomal formulations containing Celecoxib.

2^2 mathematical models have been employed for the optimization experiment in this work, which was carried out using Design Expert version 12 software. Vesicle size (Y1) and entrapment efficiency (Y2) are regarded as response variables or dependent factors, and the concentrations.

Table No: 1. Composition for the formulation of Celecoxib Transferosomes by Central Composite Design

S. No	Factor 1 A- Lipid (mg)	Factor 2 B: Surfactant/ Edge activator (ml)	Drug (Celecoxib- mg)
1	90	90	25
2	50	-6.56854	25
3	50	50	25
4	10	50	25
5	50	50	25
6	50	50	25
7	106.569	50	25
8	50	50	25
9	90	10	25
10	-6.56854	50	25
11	10	10	25
12	10	90	25
13	50	106.569	25

Particle Size and Size Distribution of Particle

The particle size distribution and vesicle size (in nm) were assessed with a Malvern Nanoparticle size analyzer. The specimens were collected using the preferred dilution of Transferosomal suspension, which had been twice deionized using distilled water. A 0.45µ membrane filter was used to filter the previously produced solution in order to conduct the research. The light dispersion's dynamic strength was determined by the device based on the medium viscosity, which was 90 degrees for low-viscosity specimens and 170 degrees for specimens with greater viscosities. This suggests that the PDI should be less than 0.7 and the Transferosomes vesicle size should be between 50 and 500 nm, as indicated by the distribution of the uniform monodisperse size. Three tests (n=3) were run in triplicate for both[13-15].

Drug Entrapment Efficiency (DEE)

Micro particles (25 mg) were pulverized and the powdered micro particles were suspended in 50 ml phosphate buffer (pH 7.4). After 24 h the solution was filtered and the filtrate was analysed by UV-VIS spectrometer (U-2001 Hitachi, Shiga, Japan) at 228 nm[15].

$$\text{DEE (\%)} = \frac{\text{Drug content as per assay x100}}{\text{Drug content as per initial load}}$$

In vitro diffusion study

In vitro permeation studies were carried out using a vertical Franz diffusion cell with a receptor compartment capacity of 100 mL, maintained at 32 ± 1 °C to simulate skin temperature. A 0.45 µm pore-size dialysis membrane was mounted between the donor and receptor compartments to prevent the leakage of vesicular components. Two milliliter of the transferosomal suspension containing 5mg (Celecoxib) were placed in the donor compartment.

The receptor chamber was filled with phosphate buffer (pH 7.4) and stirred continuously at 100 RPM using a magnetic stirrer to maintain sink conditions. At predetermined time points (0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h), 2 mL samples were withdrawn from the receptor compartment and immediately replaced with fresh buffer to maintain a constant volume. Samples were analysed using UV-visible spectrophotometry, and cumulative drug permeation was calculated using appropriate dilution correctionPhysical characterization

Fourier transforms infra-red spectroscpy (FT-IR)

FTIR Spectra have been conducted with the surfactants utilized in the formulation to ascertain the similarity profile between the medication and other constituents, including lipids. Potassium bromide (KBr) palletization was used in investigations for pure drug. 100mg samples were pulverized with dry Potassium bromide (KBr) and crushed into transparent discs and was examined by FT-IR2between 400-4000cm-1.

Differential scanning calorimetry (DSC)

It supports the confirmation of drug-excipient compatibility. DSC investigations were conducted for Celecoxib Tranferosomal formulation, utilizing the Schimadzu type instrument, DSC-70. Dry nitrogen was used as the effluent gas while a sample weighing approximately 5 mg was heated in aluminum pans at a rate of 20°C per minute, between 20 and 200°C. Using the endothermic peak shape, the melting point was determined[16].

Zeta Potential

The Malvern Nanoparticle size analyzer was used to assess the Zeta Potential, also known as the surface charge potential. The diluted Transferosomal suspensions were injected into an electrophoretic cell probe, which was subjected to an 80 mV electric field. At 25°C, both trials were done in triplicate[17].

Transmission Electron Microscopy

To ensure that the light scattering intensity remained within the sensor's sensitivity range, the transferosomal suspension was diluted with double distilled water. Copper grids with a thin carbon layer were loaded with Celecoxib transferosomal suspension for TEM imaging investigation, and they were then let to dry at room temperature. Following complete drying of the sample, the pictures were taken using a 200 Kv accelerating voltage and 0.27 nm point resolution using Transmission Electron Microscope model Philips Tecnai-20 (Philips, Holland).

RESULTS & DISCUSSION

Table no. 2. Optimization of Celecoxib Transferosomal Formulation

Run	Independent Variables			Dependent Variables	
	Factor 1 A-Lipid(mg)	Factor 2 B: Surfactant /Edge activator(ml)	Drug (Celecoxib-mg)	Vesicle Size (nm)(n=3)	Entrapment Efficiency (%)(n=3)
1	80	80	25mg	402 ±8.52	87 ±2.85
2	40	-6.56854	25mg	389±2.52	81 ±4.18
3	40	40	25mg	506±8.82	84 ±7.03
4	40	106.569	25mg	358 ±12.11	68±1.54
5	40	40	25mg	512 ±8.56	82 ±4.31
6	40	40	25mg	476 ±2.52	85 ±0.87
7	**106.569**	**40**	**25mg**	**279 ±3.01**	**92.08 ±0.23**
8	40	40	25mg	506 ±1.89	84 ±0.75
9	80	10	25mg	298 ±5.78	87 ±1.37
10	-6.56854	40	25mg	402 ±4.23	69 ±2.78
11	10	10	25mg	408 ±11.02	65 ±3.46
12	10	80	25mg	599 ±1.53	71 ±2.58
13	80	40	25mg	275 ±3.87	86 ±3.82

Based on the results of 2 major responses (Dependent variables) selected for design expert software or optimization, it was found that Formulation NTF7 of Celecoxib was found to produce more Entrapment Efficiency and optimum Vesicle Size.

***In vitro* study**

The percentage of drug released from the micro beads was dependent on the physicochemical properties of the drug and controlling variables for the preparation of micro beads like drug-polymer concentration, surfactant concentration, stirring speed etc. Polymer concentration was important variables based on viscosity of the polymer solution. Study of *in vitro* drug release profiles are displayed in Figure 22. Study of drug release was performed for all 15 runs. *In vitro* drug release was performed in SGF (2h) and SIF (16h). It was observed from these profiles that drug release (C1-C15) was varied from 58.56 to 97.60% in 18 h. There are some reports on prolonged release of GMP from microspheres upto 24 h (Mahalaxmi et al., 2009; MaCusuCan et al., 2010; Gaba et al., 2011) in which method of preparation was quite time cnsuming and expensive in cmparison with that of present investigation.

Table No .3. *In-vitro* diffusion results for Celecoxib Transferosomes NTF1-NTF6

Hrs	CBT1	CBT2	CBT 3	CBT 4	CBT 5	CBT 6
0	0	0 ±0.00	0 ±0.00	0 ±0.00	0 ±0.00	0 ±0.00
0.5	5.87 ±1.05	6.10 ±1.23	5.35 ±0.54	6.38 ±1.46	5.37 ±1.63	5.5 ±1.76
1	9.23 ±1.02	8.56 ±1.02	7.43 ±1.21	8.64 ±1.81	7.46 ±1.82	7.46 ±1.02
2	10.35 ±1.24	11.58 ±1.04	9.59 ±1.43	10.28 ±0.22	9.59 ±1.05	9.58 ±1.38
4	17.13±.1.60	18.87 ±0.57	17.75 ±1.25	17.01 ±0.79	18.02 ±0.57	17.81 ±1.81
6	25.99±1.78	30.10 ±1.02	26.71 ±0.87	25.46 ±0.08	26.55 ±0.49	26.55 ±0.85
8	35.73±1.23	37.21 ±0.21	33.43 ±0.67	31.42 ±1.05	33.43 ±0.03	33.43 ±0.56
10	46.23±0.11	50.12 ±0.32	47.54 ±0.52	48.10 ±0.92	47.54 ±0.62	47.54 ±0.33

12	62.34±0.89	64.64 ±1.45	61.43 ±0.15	65.00 ±0.45	61.43 ±0.26	61.43 ±1.55
24	82.98 ±0.91	83.84 ±1.62	81.32 ±0.56	84.01 ±0.25	81.32 ±0.41	81.32 ±0.42

Table 5.4: In vitro diffusion results for Celecoxib Transferosomes formulations F7- F13

Hrs	CBT 7	CBT 8	CBT 9	CBT 10	CBT 11	CBT 12	CBT 13
0	0 ±0.00	0 ±0.00	0 ±0.00	0 ±0.00	0 ±0.00	0 ±0.00	0 ± ±0.00
0.5	7.59 ±0.23	5.23 ±0.45	5.92 ±0.51	6.63 ±0.89	5.82 ±0.03	5.23 ±0.87	6.92 ±0.71
1	10.17 ±0.55	7.32 ±0.45	8.11 ±0.21	9.00 ±0.64	8.32 ±0.54	7.32 ±0.09	8.90 ±0.67
2	12.15 ±0.34	9.45 ±0.45	9.12 ±1.23	11.45 ±0.21	10.54 ±0.27	9.45 ±0.45	12.45 ±0.33
4	19.78 ±0.45	17.57 ±0.45	15.21 ±0.25	15.64 ±0.45	13.43 ±0.75	17.57 ±0.84	16.46 ±1.45
6	28.46 ± 1.25	26.55 ±0.45	26.85 ±0.44	27.52 ±0.31	26.21 ±0.32	27.55 ±0.34	27.21 ±1.21
8	34.14 ±0.45	33.43 ±0.45	33.91 ±0.13	31.00 ±0.23	29.88 ±0.45	33.43 ±0.11	31.43 ±0.65
10	50.95 ±0.37	47.54 ±0.45	46.84 ±0.73	45.41 ±0.42	44.87 ±0.12	47.54 ±0.46	47.72 ±0.45
12	68.75 ± 0.15	61.43 ±0.45	64.21 ±0.12	59.32 ±1.32	58.32 ±0.82	61.43 ±0.86	60.84 ±0.21
24	88.02 ± 0.22	81.32 ±0.45	83.65 ±0.61	85.52 ±0.56	83.21 ±1.45	81.32 ±0.91	86.25 ±0.15

The Franz diffusion cell is used in In vitro diffusion investigations, and the percentage cumulative drug release is computed for each formulation. F7 Out of 13 formulations exhibits the higher percentage cumulative drug release when compared with other formulations because of its maximum Entrapment Efficiency.

Fourier transforms infra-red spectroscpy (FT-IR)

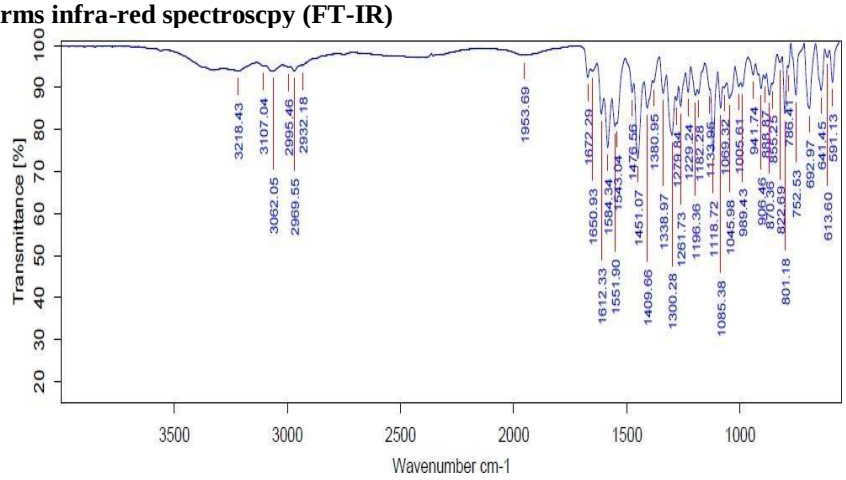

Figure 1: FT-IR Spectra of Celecoxib along with the Excipients From the FTIR spectra it was confirmed that celecoxib and formulation components were compatible with each other**.**

Differential Scanning Calorimetry (DSC)

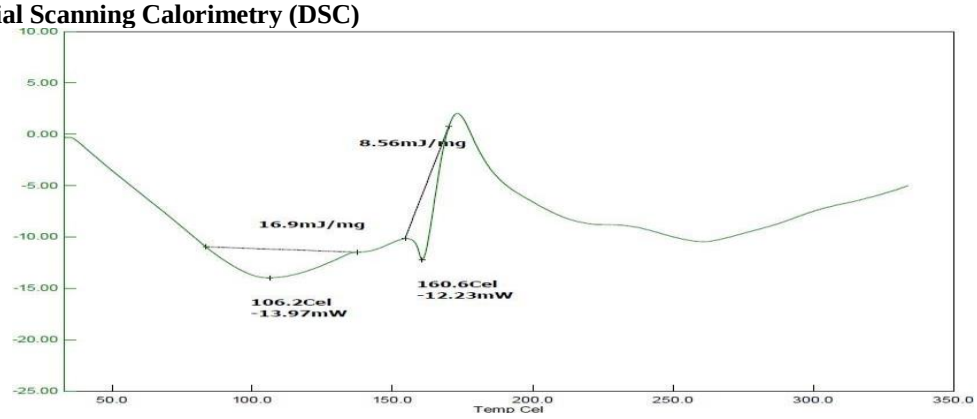

Fig. No. 2: DSC Thermogram of Optimized Celecoxib Formulation

The Pure drug and excipients employed in the formulations were found to be mutually compatible.

Zeta Potential of Celecoxib Optimized Transferosomal Foumlation

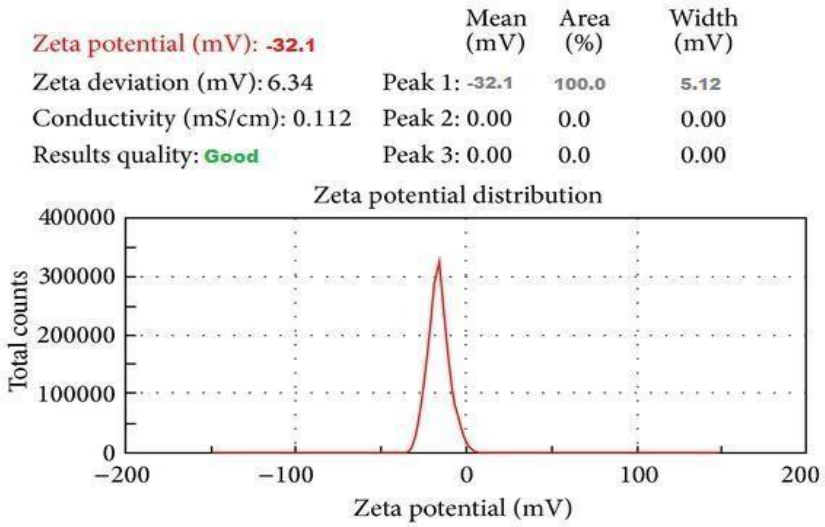

Fig No.3. Zeta Potential for Optimized Celecoxib Formulation CTG7

The optimized formulation is having a high potential value i.e. - 32.1mV. High zeta potential value contributes to the stability of the formulation and the tendency to aggregate would be minimal.

Transmission electron microscopy

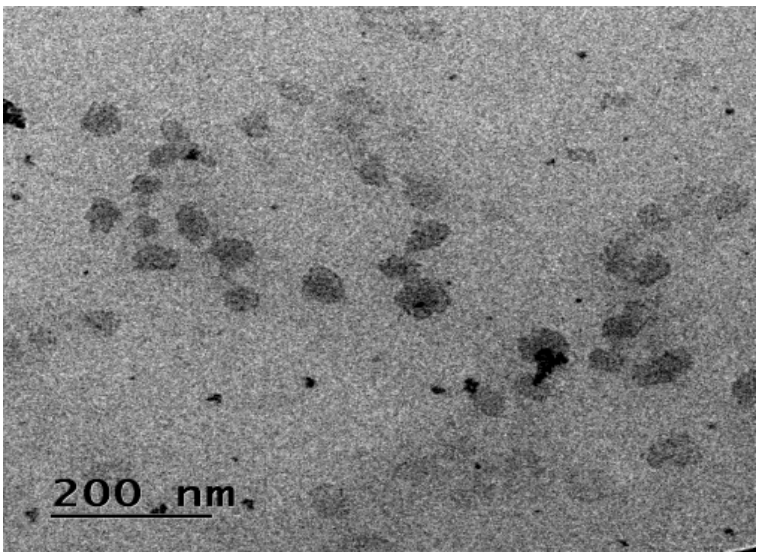

Fig. No. 4: TEM images of Optimized Celecoxib Transferosome vesicles (NTG7)

Transmission electron microscopy indicates the morphology of vesicles; the TEM pictures for CBT7 were found to be spherical with a uniform surface. The uniform surface and shape of vesicles have proved that there won't be any drug leakage happening from the formulations.

CONCLUSION:

celecoxib -loaded transfersomal gel was prepared using Thin Film Hydration mechanism. Experiments using Fourier transform infrared spectroscopy and Differential Scanning Calorimetry were used to determine drug and excipients were compatible. 2^2 mathematical models have been employed for the optimization experiment in this work, which was carried out using Design Expert version 12 software. Vesicle size (Y1) and entrapment efficiency (Y2) are regarded as response variables or dependent factors, and the concentrations of lipids (in mg) and edge activators (in ml) are treated as independent factors. optimized formulation is having a high potential value i.e. - 32.1mV. High zeta potential value contributes to the stability of the formulation and the tendency to aggregate would be minimal. The Z average of the particle size for the improved formulation is discovered to be 249.2 nm and Transmission electron microscopy indicates the morphology of vesicles; the TEM pictures for CBT7 were found to be spherical with a uniform surface. The drug release percentage of CBT7 was

88.03 ±0.22 percent over 24 hours, following a regulated and predefined release pattern.

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Conflict of Interest
The authors declare no conflict of interest, financial or otherwise.

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