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Design and Development of Ibuprofen Loaded Transferosomal Gel for Analgesic Activity

R. Divya[1], H. Gayathri[2]*, R. Tamilarasan[3], P. Indhumathi[4]
1,2*,3,4Department Of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology Kattankulathur – 603203, India

Abstract:
Aim: The aim of this research study was to formulate transferosomes containing Ibuprofen as the topical gel for the treatment of analgesic activity.
Methods: Ibuprofen is a common nonsteroidal anti-inflammatory medication. It may be administered via transferosomes, which are ultra-deformable vesicles, due to their gastrointestinal disorders. Ibuprofen transferosomes were prepared by thin film hydration method. Transferosomes were assessed using different parameters like SEM, TEM, drug content, zeta potential, invitro drug release, and stability study. Ibuprofen transferosomes were combined with Carbopol 934. The formulated transferosomal gel was evaluated for appearance, grittiness, pH, spreadability, extrudability, drug content, *invitro* drug release study and stability study.
Results: Nine transferosome formulations (F1-F9) are prepared with different ratios using a thin film hydration method. The formulated transferosomes are spherical in shape. The optimized formulation F2 containing 0.1 g Ibuprofen showed promising results having maximum drug release of 95.67% when compared to other formulations it has good stability property. Three formulations with different Carbopol 934 gel content (IG1-IG3) were prepared out of which IG3 was found to have maximum drug content 94.12% and also it showed maximum release of drug 96.78% from transferosome.
Conclusion: Ibuprofen-loaded transferosomal gel has the best analgesic effect. It is possible to conclude that transferosomes are a viable long-term delivery strategy for Ibuprofen as a topical gel with good stability.

Keywords: Transferosomes, Ibuprofen, NSAIDS, Topical gel, Analgesic activity

1. Introduction

Ibuprofen is the commonly used nonsteroidal anti-inflammatory drug (NSAID). The most well-known mechanism of action for NSAIDs, including ibuprofen, is the reversible blockade of arachidonic acid metabolism. Cyclooxygenase metabolises arachidonic acid in every cell membrane in the body. Arachidonic acid must be converted to Prostaglandin H2 (PGH2) by COX. After that, PGH2 is converted to prostaglandins. Ibuprofen inhibits COX, lowering the body's prostaglandin production. PGH2-derived prostaglandins mediate pain, fever, and inflammation. Ibuprofen may have analgesic properties due to its hypothalamic effect, which causes vasodilation, increased peripheral blood flow, and temperature regulation.

Transferosomes are ultra-flexible, self-optimizing unconventional drug carrier vesicles. Membrane flexibility, hydrophilicity, and vesicle integrity are important for their passage through the skin.

According to the current research, transferosomes are drug delivery vehicles that can pass through undamaged skin. Unhindered transit of such carriers may be attributed to the vesicle bilayers' flexibility and the skin's osmotic gradient. Transferosomes establish a transepidermal osmotic gradient and compress between stratum corneum cells to deliver drugs across the skin.

Transferosomes protect drugs against fast clearance from cutaneous blood vessels, improving circulation time and bioavailability. Transferosomes transports a wide range of chemicals, including steroids, proteins, insulin, corticosteroids, ketoprofen, and anticancer medications. They have a high

entrapment efficiency, approaching 90% for lipophilic drugs. Transferosomes are ideal candidates for the non-invasive administration of tiny, medium, and large medicines due to their deformability.

2. Preformulation Studies

A. Compatibility Study by FTIR:

FTIR spectroscopy detects drug-excipient compatibility. The IR spectra of pure drug Ibuprofen and physical mixtures of drug with excipients soya lecithin, sodium deoxycholate and Carbopol 934 was carried out by using FTIR, Nicolet. The spectra were acquired at 4000 to 500cm^{-1}.

B. Calibration curve procedure:

10 mg Ibuprofen was dissolved in 50 ml of 0.1N HCL and sonicated for 5 minutes to get the standard stock solution. Final volume of solution made up to 100ml with same solvent to get stock solution containing 100µg/ml. From the stock solution, 5, 10, 15, 20, 25µg/ml was taken by diluting to 0.5, 1, 1.5, 2 and 2.5 ml and then adding 0.1N HCL to make 10 ml. The absorbance of the solution was measured at 222nm.

Preparation

Formulation of ibuprofen loaded transferosomes

Ibuprofen, Soya Lecithin, and sodium deoxycholate were used to prepare transferosomes. In 10 ml of a mixture of two organic solvents (chloroform: methanol, 3:1 v/v), dissolve phosphatidylcholine, sodium deoxycholate, and the drug. This solution is then placed in a clean, dry bottom flask. The organic solvent was carefully evaporated using a magnetic stirrer to create a lipid layer on the flask wall. A phosphate buffer solution (pH 7.4) was hydrated by rotating for one hour at room temperature at 60 rpm and held for two hours for swelling. Using a probe sonicator, multilaminar lipid vesicles (MLV) are sonicated for 10 minutes (Heidolph vcx750). Using a cooled ultracentrifuge and high-speed centrifugation at 10,000 rpm for 1 hour, the Ibuprofen transferosomes would be separated from the trapped Ibuprofen. Clear supernatant will be carefully taken out after centrifugation to isolate the trapped Ibuprofen. The precipitate will be suspended in 10 ml of phosphate buffer for evaluation (pH 7.4).

Table 1: Formulation Batches of Ibuprofen loaded transferosomes

Formulation code	Ibuprofen (mg)	Phosphatidylcholine (mg)	Sodium deoxycholate (mg)	Solvent mixture (Chloroform:Methanol) (ml)
F1	100	60	40	1
F2	100	60	40	2
F3	100	60	40	3
F4	100	60	60	1
F5	100	60	60	2
F6	100	60	60	3
F7	100	30	60	1
F8	100	30	60	2
F9	100	30	60	3

Method for Preparation of Gel

Carbopol-934 of three different formulation (250, 500 and 1000 mg) were dispersed in 15-30ml of distilled water and the mixture was blended until thickened. Add PEG 400 gently to the Carbopol 934 dispersion. Then, isopropyl alcohol (IPA), propylene glycol (PG) and triethanolamine are mixed until

a gel develops and finally the drug was added to the prepared transferosomal formulation, and it has been evaluated with different parameters.

Table 2: Formulation of Ibuprofen Transferosomal Gel

S.NO	Ibuprofen Transferosome (mg)	Carbopol (mg)	Triethanol Amine (ml)	Propylene Glycol (ml)	Iso-Propyl Alcohol (ml)	Water (ml)
IG1	100	250	10	5	5	Q.S
IG2	100	500	10	5	5	Q.S
IG3	100	1000	10	5	5	Q.S

Evaluation of transferosomes

1. Transmission electron microscopic studies:

The formulated transferosomes can be determined for their shape by using transmission electron microscopic studies.

2. Scanning electron microscopic studies:

The morphology of surfaces is studied using scanning electron microscopic techniques.

3. Percentage Drug Content:

1 g of transferosomes were sonicated for 15 minutes in 25 ml of ethanol. This solution was centrifuged for 30 minutes at 10,000 rpm. With phosphate buffer pH 7.4, a 10 ml clear solution was diluted to 100 ml. Aliquots were withdrawn and Ibuprofen drug content was measured at 222nm.

4. Zeta Potential Analysis:

Zetasizer measures vesicle diameter, size distribution, and zeta potential. Photon correlation spectroscopy (PCS) was used at a constant angle of 90° at 25 °C using water as a dispersant to measure transferosome particle size and zeta potential.

5. Invitro Drug Release Studies:

The invitro permeation of ibuprofen from all transferosomes formulations and cellophane membrane were examined. For permeation studies, a vertical Franz diffusion cell was used. Cellophane was affixed to a 2 cm^2 diffusion cell. The receptor compartment contained 30 ml pH 7.4 phosphate buffers and was kept at 37 ± 0.5°C with 100 rpm agitation. Formulation applied to donor compartment membrane. At intervals, 2 ml samples were removed and replaced with fresh diffusion medium. The cumulative cellophane membrane permeability was plotted over time.

6. Stability Studies

Based on the drug content, stability investigations were done at 25 ± 2°C for 30 days.

Evaluation for Ibuprofen Gel

1. Appearance: -

The formulation of carbopol gel was developed and its physical appearance was visually evaluated.

2. Grittiness:

The light microscope was used to detect particles in all formulations. The gel composition is free of grit and particular matter, which is ideal for topical formulations.

3. PH Value Of Topical Transfersome Gel:

A digital pH metre was utilised in order to ascertain the pH value of the various gel formulations.

4. Spreadability test:

One glass slide held the gel formulation, which contained 350 mg, while a second glass slide, which was positioned 5 cm away, held around 5.8±1g of gel. After one minute, the spread gel circle's diameter was measured and the results can be determined with the following table:

Table 3: Types of Gels and their values of spreadability

S. NO	TYPE OF GEL	SPREADABILITY
1	Fluid	> 2.4
2	Semi-fluid	1.9 - 2.4
3	Stiff	1.6 – 1.4
4	Semi-stiff	1.9 – 1.6
5	Very stiff	< 1.4

5. Extrudability Test:

After determining the weight in grams needed to extrude at least 0.5 cm of gel in 10 seconds, the gel quantity (g/cm^2) was extruded from the lacquered aluminium collapsible tube. The extrudability can be calculated using the formula:

$$\text{Extrudability} = \frac{\text{Weight applied to extrude gel from the tube (g)}}{\text{Area in cm}^2}$$

6. Drug Content:

1 g of transferosome gel was utilised, and the vesicles were sonicated for 15 minutes in 25 ml of methanol. It was then centrifuged at 10,000 rpm for 30 minutes. The solution was diluted with 100 ml pH 7.4 phosphate buffer. The drug content of Ibuprofen was determined using a UV spectrophotometer set to 222 nm.

7. Invitro Release Study:

An exact amount of formulation is dispersed on a membrane with a diffusion area between the donor and receptor chambers (Franz-diffusion cell apparatus). The receptor compartment is continually swirled with a tiny magnetic bar at 50 rpm with phosphate buffer pH 6.8. At regular intervals, samples are extracted and replaced with the same volume of phosphate buffer solution. A spectrophotometer was used to analyse the samples.

8. Stability Study:

Stability testing was conducted at room temperature (25 ± 2°C) for two months. The pH, spreadability, and extrudability of the formulation were evaluated after the first two months.

3. Results And Discussion

Preformulation Studies

A. Drug-Excipient Compatibility study through FTIR

IR spectrophotometry has been used to identify drug-excipient interactions. The figures below show the IR spectrum of ibuprofen when it is physically combined with soy lecithin, phosphatidylcholine, sodium deoxycholate, and carbopol 934. The IR spectra show no interactions between the drug and excipients. The peaks are same in both the spectra. So, the excipients seems to be compatible.

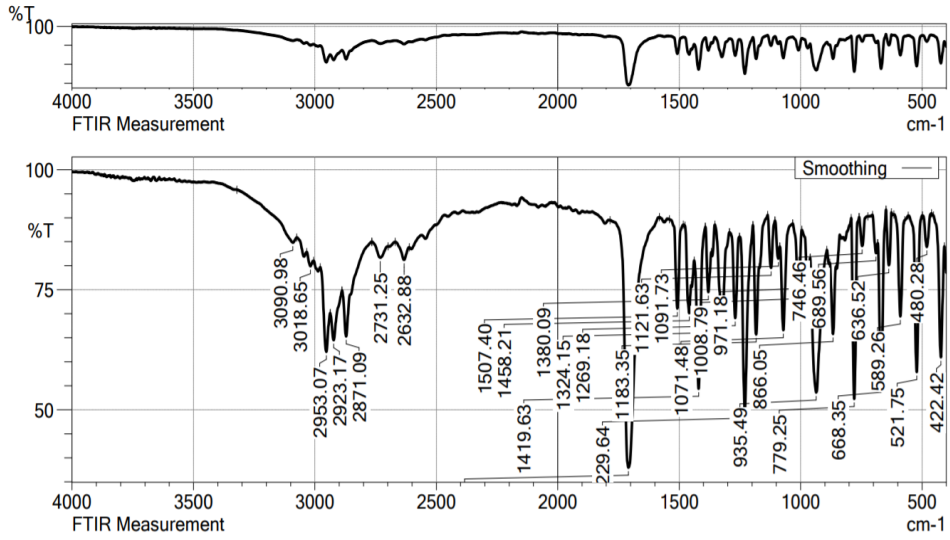

Figure 1: FTIR Spectra of Ibuprofen Pure Drug

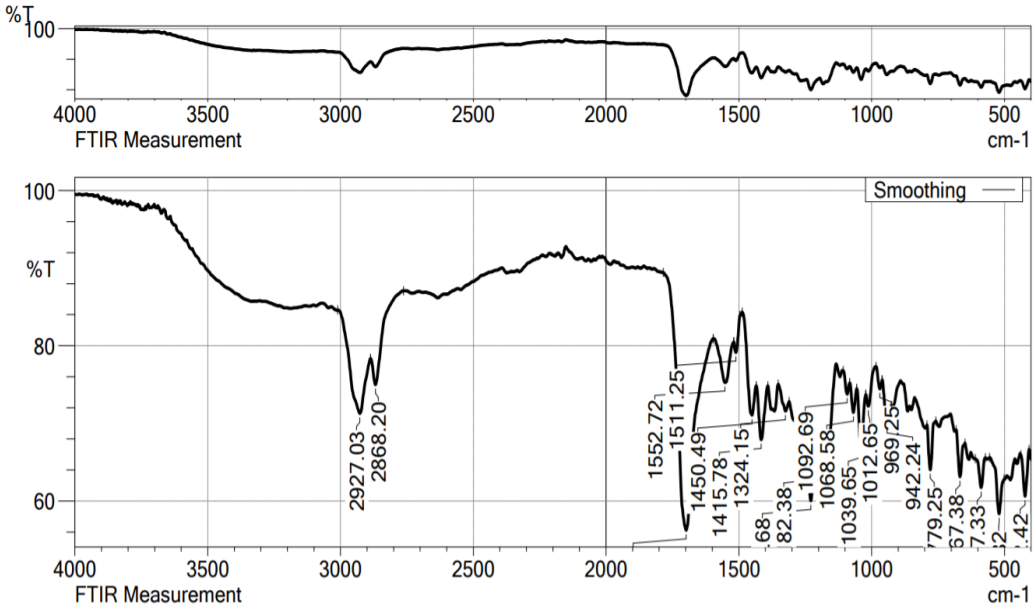

Figure 2: FTIR Spectra of Ibuprofen with excipients soya lecithin, Phosphotidylcholine, Sodium deoxycholate and Carbopol 934

B. Standard Curve of Ibuprofen

The maximum absorption of ibuprofen in 0.1 N HCL was found to occur at a wavelength of 222nm and all obtained values are given in the table 4. At a given concentration the standard curve obtained for the drug ibuprofen obeys Beer's law. The relationship between absorbance and concentration is found to be linear, having a regression coefficient value of 0.9996 when subjected to regression analysis.

Table 4: Calibration Curve of Ibuprofen

S.NO	CONCENTRATION (mcg/ml)	ABSORBANCE 222nm

1.	0	0
2.	5	0.126
3.	10	0.256
4.	15	0.398
5.	20	0.523
6.	25	0.667

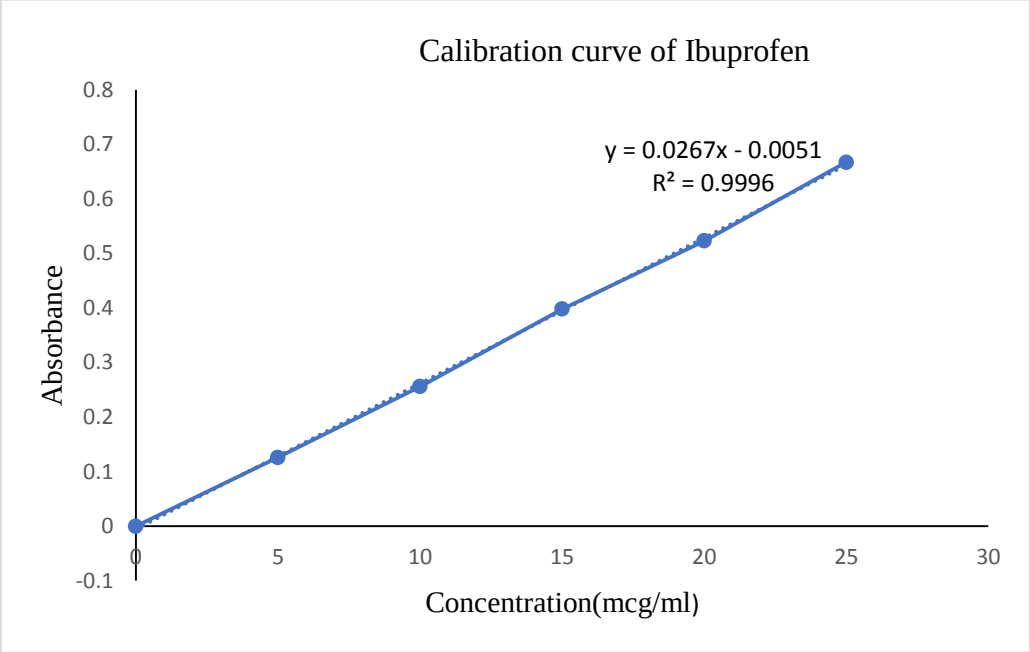

Figure 3: Calibration Curve of Ibuprofen

Evaluation of ibuprofen loaded transfersomes

1. Transmission electron microscopy:

Transmission electron microscopy was used to examine the surface's morphology. Most transferosomes containing ibuprofen were found to have a spherical shape. The transmission electron micrograph of the examined transferosome (F2) revealed the outline and core of the spherical vesicles, indicating the generated transferosome's vesicular properties as shown in Figure 4.

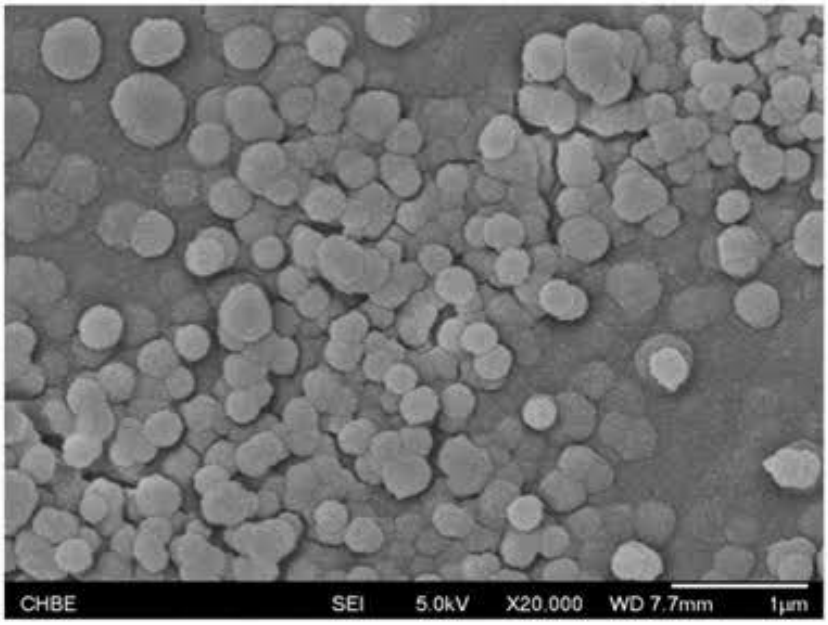

Figure 4: TEM Micrograph of Transfersomal Formulation F2

2. Scanning Electron Microscopy:

The shape of the formulated transferosomes was determined using scanning electron microscopy. The morphological structure found was spherical in shape as shown in Figure 5.

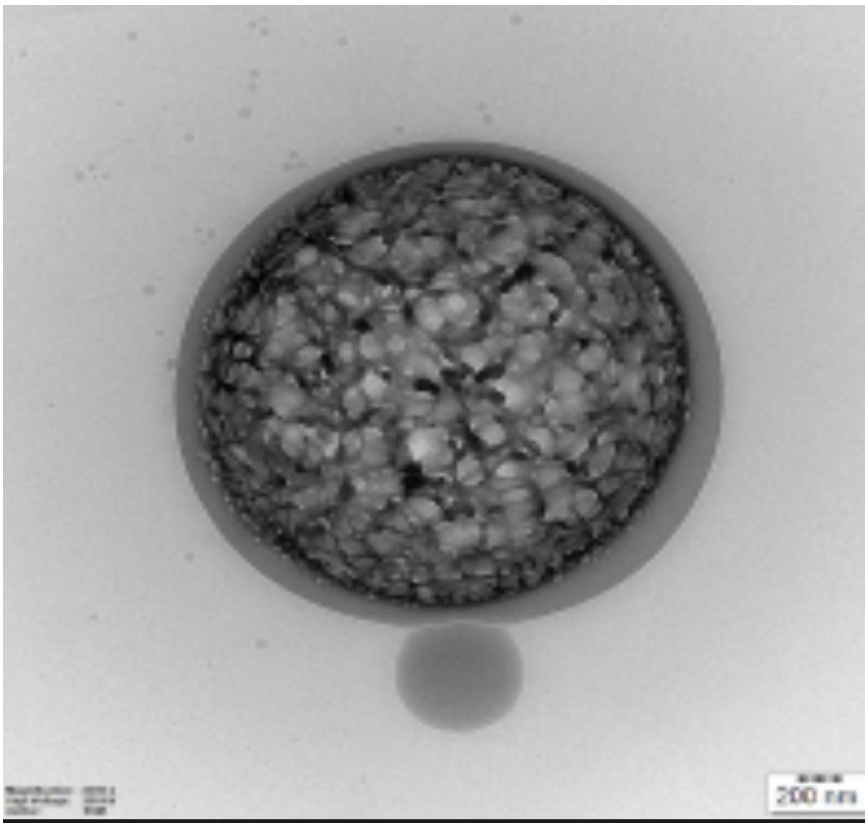

Figure 5: SEM Micrograph of Transfersomal Formulation F2

3. Percentage Drug Content:

The results determined shows 80.32 – 95.12% drug content in the six different formulations prepared (Figure 6). Drug is not degraded in the process which can be seen from the results obtained. From the results it is indicated that the process employed to prepared different batches of transferosomes is compatible showing a constant drug content.

Table 5: Evaluations of Transferosomes for Drug Content

S.NO	FORMULATION	% DRUG CONTENT
1.	F1	86.34± 0.04
2.	F2	95.12± 0.05
3.	F3	89.16± 0.08
4.	F4	84.25± 0.03
5.	F5	80.32± 0.07
6.	F6	91.63± 0.02
7.	F7	85.07± 0.01
8.	F8	83.45± 0.04
9.	F9	85.97± 0.06

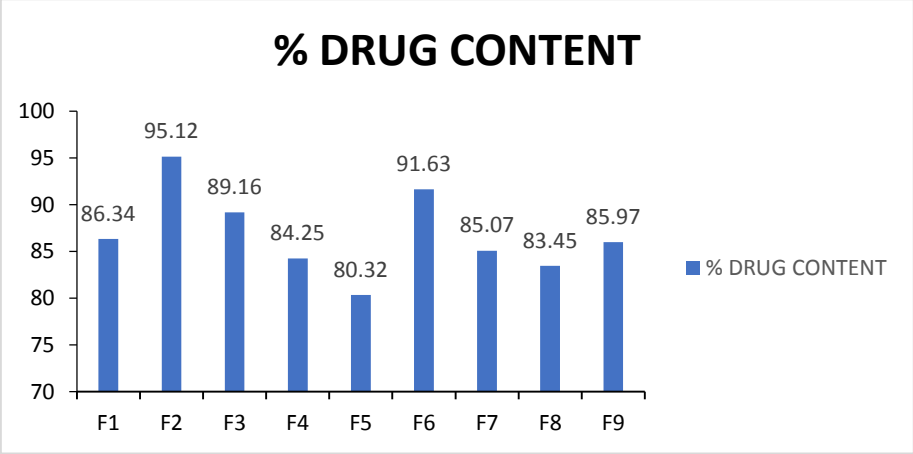

Figure 6: % Drug content of all formulations

4. Particle Size & Zeta Potential Analysis

The light scattering method using Zetasizer was utilised to determine the optimised formulation's zeta potential, size distribution, and vesicle size (DTS Version 5.03, Malvern). The vesicle's average diameter was measured to be 632.5 nm.

Table 6: Zeta average size and PDI of optimized formulation

FORMULATION	ZETA-AVERAGE SIZE	PDI
F2	632.5 nm	0.796

The size distribution curve depicts the normal size and distribution of vesicles.

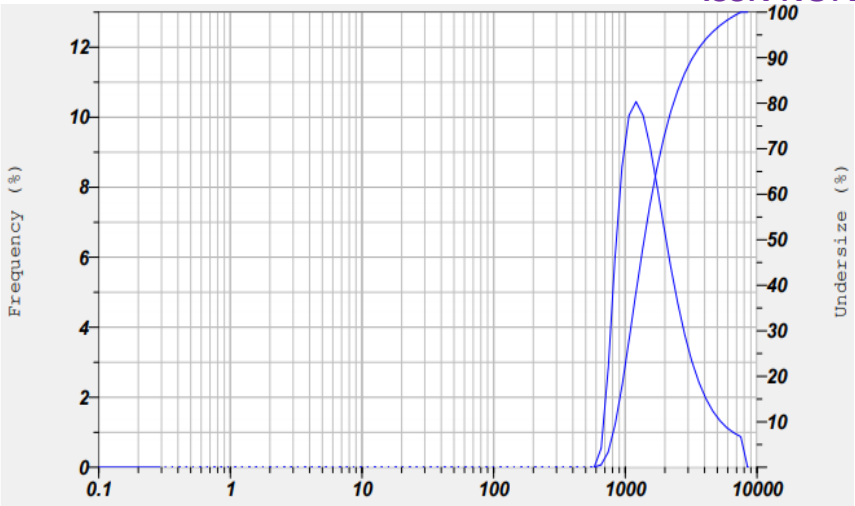

Figure 7: Vesicle Size of Optimized Transferosomes Formulation F2

5. Invitro Drug Release Studies:

Using a cellophane membrane, each Ibuprofen transferosome formulation was tested for in vitro drug release tests. The cumulative amount of drug released was calculated for each formulation. In comparison to other Ibuprofen transferosome formulations, the F2 formulation showed the largest cumulative level of drug release (95.67%) up to 6 hours. The rate of Ibuprofen release from F2 was significantly higher than that of the other formulation (Figure 8). The release studies showed controlled-release of Ibuprofen from transferosomes. Based on the findings, Ibuprofen transferosomes (F2) can be considered as a good alternative method for reducing dosage frequency and also maintaining drug concentration at desired site of application.

Table 7: *In-vitro* Release Study of Transferosomal Formulations (F1-F9)

TIME IN HOURS	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.25	20.97	28.34	25.76	23.53	24.39	24.54	25.32	22.76	23.97
0.5	33.07	38.63	30.17	29.71	31.28	30.05	30.23	32.92	32.44
1	41.53	46.22	39.82	38.31	40.72	37.63	38.47	42.61	43.68
2	61.32	66.74	58.82	58.37	54.52	59.42	60.33	57.22	58.42
4	74.51	80.61	79.56	75.51	76.72	76.17	77.89	78.56	75.47
6	87.08	95.67	91.05	88.35	86.17	90.01	88.36	89.42	87.29

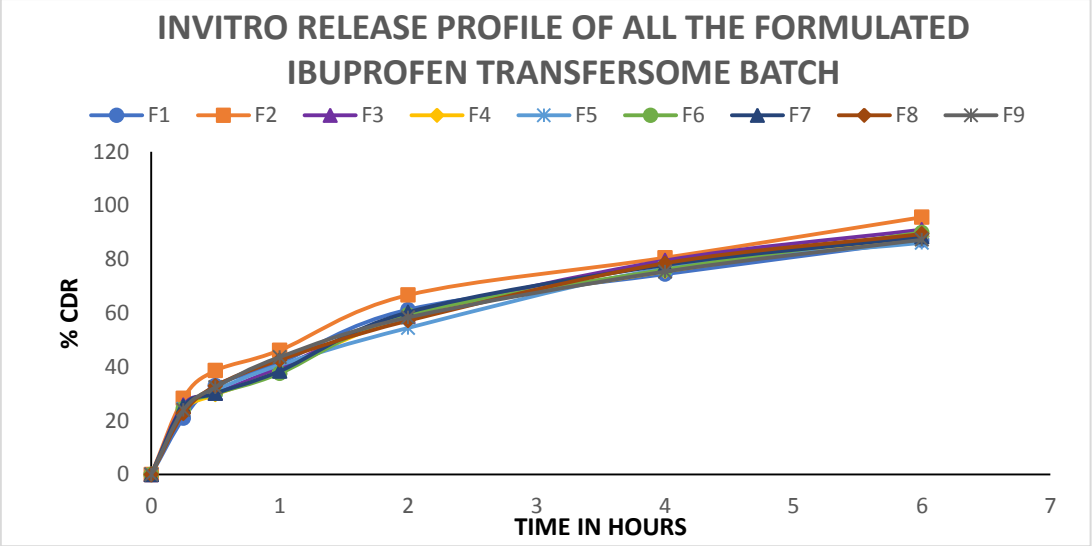

Figure 8 : *Invitro* Release Profile of all the Formulated Ibuprofen Transferosome Batch

6. Stability Studies

The stability studies were carried out according to drug content at 25 ± 2° C for a period of 30 days. It is clear from the results obtained that the transferosomes have shown the minimum drug loss at room temperature, and fairly high retention of the drug inside the vesicles was observed. At this temperature condition drug content was good over a period of 30 days.

Table 8: Percentage Drug Content after Stability Studies

Number of days	**% Drug content**	
30 days	Before (25 ± 2° C)	After (25 ± 2° C)
	95.12± 0.05	93.32±0.987

n = S.D ± 3 n = S.D ± 3

Incorporation Of Transferosomal Drug Formulation In Carbopol 934 Gel

Transferosomes dispersion was mixed with Carbopol gel. Finally, using a mechanical stirrer, transferosomal dispersion (free of unentrapped drug) was incorporated into Carbopol 934 gel for 5 minutes. The best batch of Carbopol gel will be chosen through drug content and invitro release experiments among the three batches that have been formulated.

Evaluation Of Transfersomal Gel:

1. Appearance:

The appearance of the three differently formulated nanogels was tabulated in table 9.

Table 9: Appearance of Transferosomal Gel Batches

S. NO	**FORMULATION CODE**	**APPEARANCE**
1.	IG1	White and opaque
2.	IG2	Highly viscous
3.	IG3	Clear and soft

2. Grittiness:

The developed gel preparations fulfilled the requirements of freedom from particular matter none of the formulations showed grittiness and the results are:

Table 10: Grittiness of 3 different Gel Batches

S. NO	FORMULATION CODE	GRITTINESS
1	IG1	No
2	IG2	No
3	IG3	No

3. PH Value Of Topical Transferosome Gel:

The pH of topical transferosome gels was determined using a digital pH metre at room temperature. For skin delivery of a drug to understand its suitability, the pH of the formulation is given major importance. A pH range of 6.8-7 was determined for the three various formulations prepared, of which the optimised formulation IG3 had a pH value of 6.8.

Table 11: pH value of Gel

S.NO	FORMULATION CODE	pH
1	IG1	7.0± 0.7
2	IG2	6.9± 0.5
3	IG3	6.8± 0.8

n = S.D ± 3

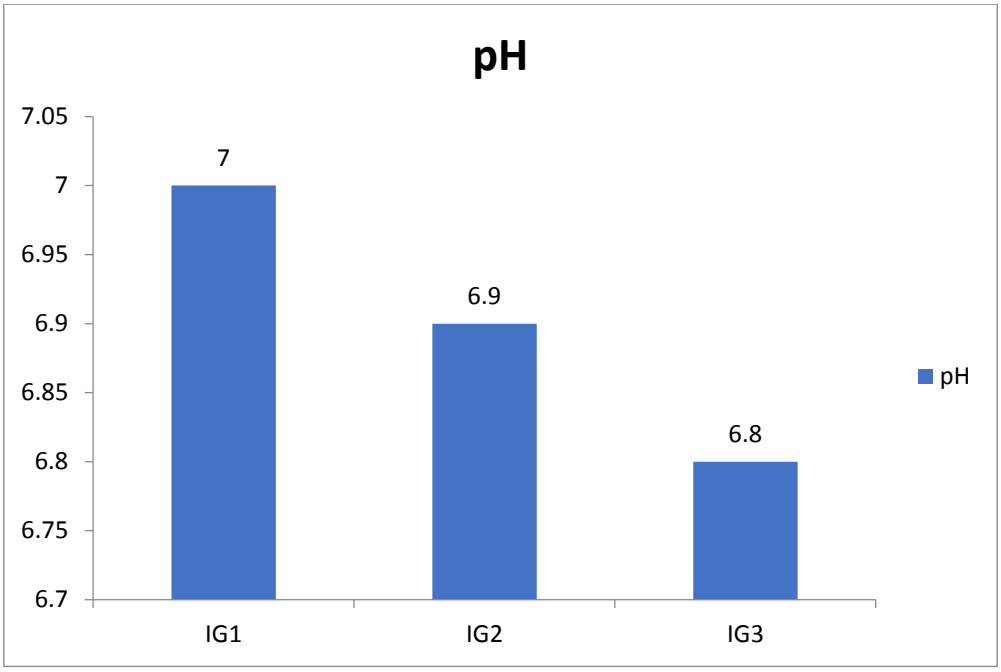

Figure 9: pH of all Formulations

4. Spreadability Test:

Spreadability was determined using a modified apparatus. The spreadability of the gels was assessed using slip and drag characteristics and ranged from 1.70 to 3.76 gm.cm/sec. The spreadability of optimised formulation IG3 was determined to be 1.70, indicating good spreadability.

Table 12: Spreadability of three different Gel Formulations

S. NO	FORMULATION CODE	SPREADABILITY (Gm.cm/sec.)
1	IG1	3.76 ± 0.5
2	IG2	2.06 ± 0.1
3	IG3	1.70± 1.9

n = S.D ± 3

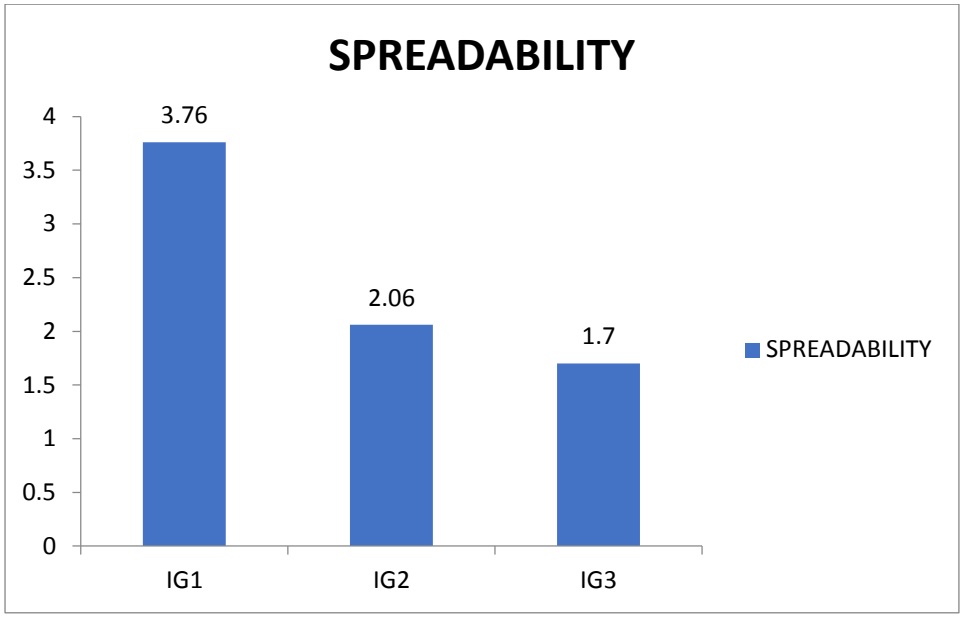

Figure 10: Spreadability of all Formulations

5. Extrudability Test:

Extrudability of various batches increased with increase in Carbopol concentration. The three formulations varied in values from 5.5 ± 0.25 to 7.7 ± 0.20. The batch IG3 showed good extrudability of 6.2 ± 0.20.

Table 13: Extrudability Values of 3 Different Gel Batches

S. NO	FORMULATION CODE	EXTRUDABILITY
1	IG1	5.5±0.25
2	IG2	7.7±0.20
3	IG3	6.2±0.20

n = S.D ± 3

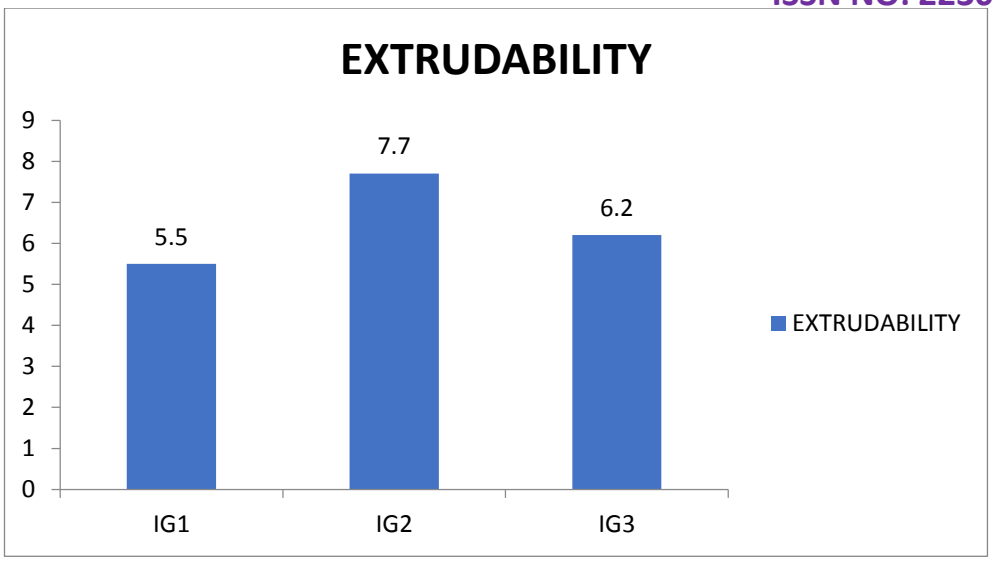

Figure 11: Extrudability of all Formulations

6. Drug Content:

The most important in transferosomal formulation is drug content and the data found are satisfactory. It was found to be 83.06 to 94.12 % which shows the good capacity of formulation to hold the drug. The maximum drug content was found in formulation IG-3 (94.12 %) as given in table 14.

Table 14: Drug Content of different Gel Formulations

S. NO	FORMULATION	% DRUG CONTENT
1	IG1	87.38 ± 0.85
2	IG2	83.06±0.05
3	IG3	94.12±0.91

n = S.D ± 3

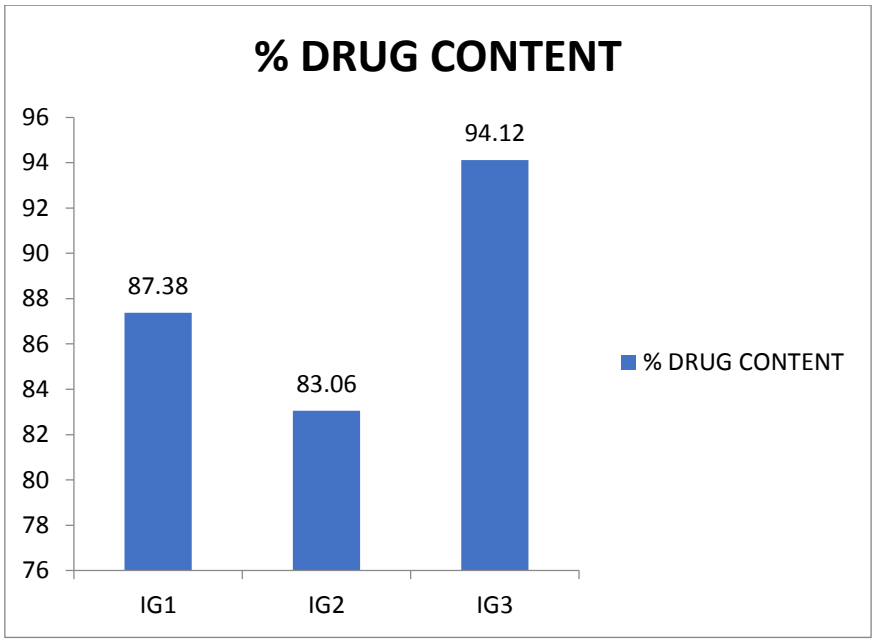

Figure 12: Drug content of all Formulations

7. Invitro Drug Release:

Transferosome gels (IG1, IG2, and IG3) were examined invitro for 6 hours in phosphate buffer pH 7.4 using a modified Franz diffusion cell with a dialysis membrane. The results of diffusion studies have been summarised. Drug release from transferosomes gel follows IG3>IG1>IG2.

Table 15: Invitro Drug Release of different Gel formulations

TIME IN HRS	IG1	IG2	IG3
0	0	0	0
0.25	24.72	23.46	27.14
0.5	34.16	32.67	36.52
1	45.87	43.38	47.28
2	61.03	59.92	65.39
4	76.47	75.03	78.17
6	94.32	92.17	96.78

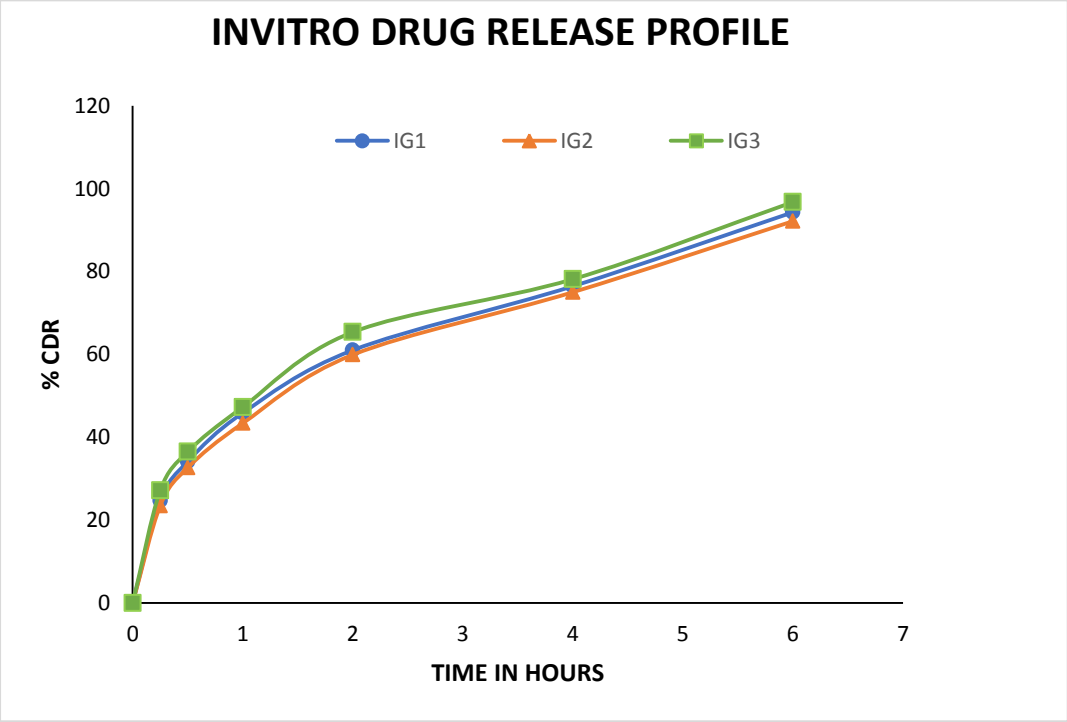

Figure 13: *In-vitro* Drug Release Study of all three Gel Formulations

8. Stability Study:

The stability study was carried out for a period of two months in room temperature for the batch IG3. The results showed that there was not much variation with the results within the period of two months. The results are shown in the table 16.

Table 16: Stability Studies for pH, Spreadability and Extrudability of IG3 Batch

Evaluation	Initial	1st month	2nd month
pH	6.8 ± 0.8	6.7 ± 0.9	6.7± 0.7
Spreadability	1.70 ± 1.9	1.64 ± 0.19	1.63 ± 0.82

Extrudability	6.2 ± 0.20	6.1 ± 0.81	6.0 ± 0.12

n = S.D ± 3

4. Conclusion

In the above evaluation it was found that Ibuprofen loaded transferosomal gel has the optimal size and zeta potential for skin penetration. Thus, optimized transferosomes formulation F2 shows promising results having maximum drug release (95.672 %) and maximum drug content (95.12 %) when compared to other formulations. Then it was successfully added to Carbopol gel and tested for pH, grittiness, spreadability, extrudability, drug content, invitro drug release, and stability. Three formulations with different Carbopol gel content were prepared out of which IG3 showed better results having the maximum drug content (94.12 %) and also it showed maximum release of drug from transferosome (96.78 %). Therefore, IG3 sample with Ibuprofen loaded transferosomal gel shows the best effect on analgesic activity. From the study, it can be stated that transferosomes are a promising prolonged delivery strategy for Ibuprofen as a topical gel and have reasonably good stability characteristics.

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Author's contributions
All the authors contributed equally.

Conflict Of Interests: Declared none

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