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FORMULATION AND EVALUATION OF TRANSFEROSOMAL GEL OF UPADACITINIB FOR TARGATED ANTI INFLAMMATORY THERAPY

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Abstract:

The present study was undertaken to formulate and evaluate an upadacitinib-loaded transferosomal gel for transdermal drug delivery with the objective of improving skin penetration, providing sustained drug release, and enhancing localized anti-inflammatory therapy. Upadacitinib is a selective Janus kinase-1 inhibitor with anti-inflammatory and immunomodulatory activity; however, its poor aqueous solubility presents a challenge for formulation development. Transferosomes, owing to their highly deformable vesicular structure, were selected as a suitable carrier for enhancing drug delivery across the skin. Upadacitinib-loaded transferosomes were prepared by the thin-film hydration method using soya lecithin, cholesterol, and Span 80. Eight formulations (F1–F8) were developed with different concentrations of soya lecithin and Span 80 and were evaluated for particle size, zeta potential, vesicle morphology, percentage yield, and entrapment efficiency. The optimized transferosomal dispersion was subsequently incorporated into a Carbopol 934 gel base and subjected to further evaluation. The prepared transferosomes showed particle sizes ranging from 172 to 275 nm, with zeta potential values ranging from −22 to −33 mV. Formulation F5 exhibited the smallest particle size (172 nm), highest negative zeta potential (−33 mV), highest percentage yield (91.2%), and highest drug entrapment efficiency (93.87%), indicating favorable vesicular characteristics. The transferosomal vesicles were further characterized by SEM to assess their morphology and surface characteristics. The optimized transferosomal gel formulation demonstrated sustained drug release, with formulation F6 showing 98.73% cumulative drug release at 12 hours. The release data fitted best to the Higuchi model with an R^2 value of 0.989, indicating that diffusion was the predominant mechanism of drug release. Stability studies conducted for three months under 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH showed only a slight reduction in drug release, with values remaining above the specified limit of 85%. Overall, the findings indicate that the developed upadacitinib transferosomal gel possesses desirable vesicular characteristics, high drug entrapment, sustained drug release, and satisfactory stability, suggesting its potential as a promising topical/transdermal delivery system for upadacitinib.

Keywords: *Soya lecithin, FTIR studies, Thin film hydration method, Transferosomes, Gel, In vitro drug release studies*

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INTRODUCTION:

Topical and transdermal drug delivery systems offer several potential advantages, including avoidance of gastrointestinal exposure and first-pass hepatic metabolism, improved patient convenience, localized drug delivery, and the possibility of sustained drug release.[1] Vesicular drug-delivery systems have therefore received considerable attention as carriers for enhancing dermal and transdermal drug transport. Among these systems, transfersomes are highly deformable and elastic lipid vesicles primarily composed of phospholipids and an edge activator.[2] Transfersomes possess several characteristics that make them attractive for topical drug delivery, including high vesicular flexibility, the ability to incorporate drugs with different physicochemical properties, potential enhancement of skin penetration, protection of encapsulated drugs, and the possibility of controlled or sustained drug release.[3] Incorporation of transfersomal vesicles into a suitable gel base can overcome these limitations. A transfersomal gel combines the penetration-enhancing properties of ultradeformable vesicles with the desirable rheological and application characteristics of a semisolid dosage form.[4] The gel matrix can improve spreadability, retention at the site of application, patient acceptability, and residence time while providing a suitable vehicle for controlled drug delivery.[5] The prepared upadacitinib-loaded transfersomes can be characterized for vesicle size, zeta potential, morphology, entrapment efficiency, drug content and in-vitro drug release. Following incorporation of the optimized transfersomal formulation into a gel base, the resulting formulation can be evaluated for physical appearance, homogeneity, pH, viscosity, spreadability, drug content, in-vitro drug release, and stability.[6] Inflammation is a complex biological response of vascularized tissues to harmful stimuli such as pathogens, damaged cells, irritants, and immune-mediated injury. Although inflammation is an essential protective mechanism, excessive or persistent inflammatory responses contribute to the development and progression of numerous acute and chronic disorders.[7] Upadacitinib is a synthetic small-molecule Janus kinase (JAK) inhibitor used in the management of several immune-mediated inflammatory diseases.[8] Thus, the present investigation is aimed at the formulation and evaluation of an upadacitinib-loaded transfersomal gel for targeted anti-inflammatory therapy. The study may provide a basis for the development of an effective vesicular topical delivery platform for upadacitinib in the management of inflammatory conditions.

MATERIALS

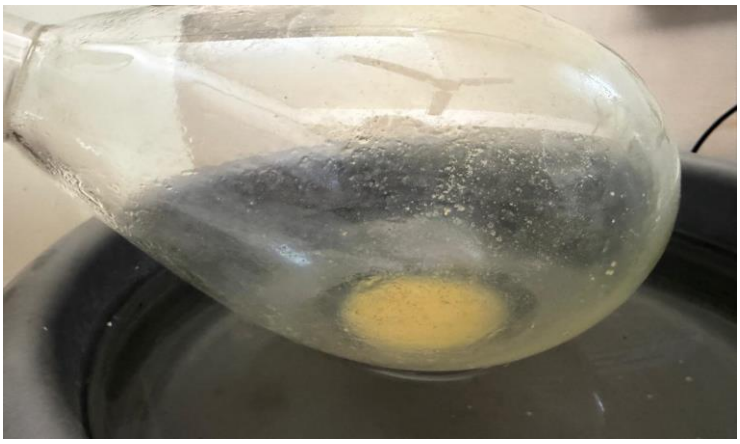
Upadacitinib was procured from Hetero Labs, Hyderabad. Soya lecithin, Cholesterol and Span 80 were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Formulation development

Table-1: Formulation table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Upadacitinib(mg)	10	10	10	10	10	10	10	10
Soya lecithin(mg)	100	100	100	200	200	200	300	300
Cholesterol(mg)	20	20	20	20	20	20	20	20
Span 80(mg)	20	40	60	20	40	60	20	40
Chloroform(ml)	10	10	10	10	10	10	10	10
Methanol(ml)	5	5	5	5	5	5	5	5



Preparation method transferosomes

Transferosomes containing Upadacitinib were prepared by the thin film hydration method using different concentrations of soya lecithin as shown in formulations F1–F8. Accurately weighed quantities of Upadacitinib, soya lecithin, cholesterol, and Span 80 were dissolved in a mixture of chloroform and methanol (2:1 ratio) taken in a clean, dry round-bottom flask. The organic solvents were evaporated under reduced pressure using a rotary vacuum evaporator at 40–45°C until a thin lipid film was formed on the inner wall of the flask. The formed film was further dried to remove traces of solvent completely.

The dried lipid film was then hydrated with phosphate buffer pH 7.4 while rotating the flask gently to obtain vesicular dispersion. Hydration was continued for about 1 hour to allow complete swelling of the lipid film. The resulting suspension was kept for maturation at room temperature for a suitable period. The obtained transferosomal dispersion was then sonicated using a probe sonicator or bath sonicator for a few minutes to reduce vesicle size and obtain uniform transferosomes. Finally, the prepared transferosomal formulations (F1–F8) were collected and stored in sealed containers under refrigerated conditions for further evaluation studies.[9]

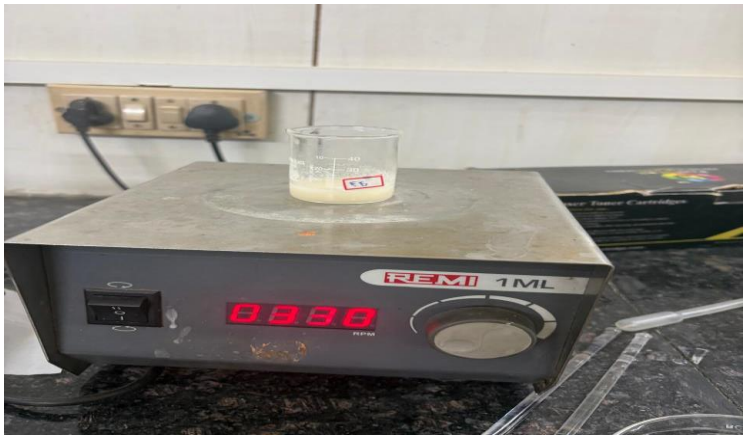
Incorporation into gel base (Carbopol gel)

Table-2: Formulation development of transferosomal gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Optimized formulation of Transferosomes (F5)	5	5	5	5	5	5	5	5
Carbopol 934 (mg)	100	200	300	400	500	600	700	800
Methyl paraben (ml)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Glycerine (ml)	1	1	1	1	1	1	1	1
Water	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

Prepare Carbopol gel base[10]

Transferosomal gel formulations of Upadacitinib were prepared using Carbopol 934 as the gelling polymer. Required quantities of Carbopol 934 for formulations F1–F8 were accurately weighed and dispersed slowly in distilled water with continuous stirring to obtain a uniform dispersion. The polymer dispersion was allowed to hydrate and swell completely for about 24 hours to form a clear gel base. Methyl paraben was added as a preservative, and glycerine was incorporated into the hydrated Carbopol dispersion to improve smoothness and consistency of the gel. The mixture was stirred continuously until a homogeneous gel base was formed. Separately prepared transferosomal suspension (5 mL) was then added slowly into the gel base with gentle stirring to ensure uniform distribution of transferosomes throughout the formulation. The pH of the gel was adjusted to skin-compatible pH using triethanolamine until a smooth and transparent gel was obtained. The prepared transferosomal gel formulations were packed in suitable airtight containers and stored for further evaluation studies.





CHARACTERIZATION

Particle Size

The particle size of the Transferosomes were determined using Particle Size Analyzer (PSA) with the dynamic light scattering (DLS) method. The measurements were performed using Horiba Scientific SZ-100, with the sample diluted 10 times in aqueous medium at room temperature.[11]

Zeta-potential:

The sample was diluted with distilled water (1:100 (V/V)) and zeta potential was determined using Malvern zetasizer (Nano ZS, Malvern Instruments, United Kingdom). Measurement was based on the electrophoretic mobility of the particles, which was converted to the zeta potential by inbuilt software based on the Helmholtz-Smoluchowski equation.[12]

SEM analysis

The shape, surface characteristics, and size of the Transferosomes were observed by scanning electron microscopy. Once again, 0.2 g of the Transferosomes in a glass tube was diluted with 10 ml of pH 7.4 phosphate buffer. The Transferosomes were mounted on an aluminium stub using double-sided adhesive carbon tape. Then the vesicles were sputter-coated with gold palladium (Au/Pd) using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Hitachi 3700N, Germany) equipped with a digital camera, at 10 kV accelerating voltage.[13]

EVALUATION PARAMETERS OF TRANSFEROSOMAL GEL[14,15,16]

Physical evaluation:

The formulation was manually examined to check any variations in the color, odor, and texture.

Measurement of pH:

PH of each formulation was determined by using pH meter. This was calibrated before with buffer solutions.

Determination of viscosity:

The viscosity measurement of Transferosomal gels was determined by using a Brookfield viscometer. 30gm of gel preparation was kept in 50ml beaker, set at room temperature and spindle at 5, 10, 20, 50, and 100rpm.

Spread ability

Two sets of glass slides of standard dimensions were taken. The transferosomal gel formulation was placed over one of the slides. The other slide was placed on the top of the gel, such that the gel was sandwiched between the two slides in an area occupied by a distance of 7.5 cm along the slides. 1g weight of gel was placed on the upper slides so that the gel was between the two slides was pressed uniformly to form a thin layer. The weight was removed and the excess of gel adhering to the slides was scrapped off. The two slides in position were fixed to a stand without slightest disturbance and in such a way that only upper slides to slip off freely by the force of weight tied on it. A 200mg weight was tied to the upper slide carefully. The time taken for the upper slide to travel the distance of 7.5 cm and separated away from the lower slide under the influence of the weight was noted. The experiment was repeated for three times and the mean time was taken for calculation.

Spread ability was calculated by using the following formula: $S = m \times l/t$

where,

S= spread ability, m-weight tied to upper slides (1 g),

l- Length of the glass slide (7.5 cm), t- time taken in sec.

Drug entrapment efficiency

Each formulation (1 g) was taken in a 50 mL volumetric flask and made up to volume with 7.4 phosphate buffer and shaken well to dissolve the active constituents in 7.4

phosphate buffer. The solution was filtered through Whatman filter paper and 0.1 mL of the filtrate was pipetted out and diluted to 10 mL with 7.4 phosphate buffer. The content of active constituents was estimated spectro photometrically by using standard curve plotted.

In vitro diffusion profile

In vitro release study of the formulated Transferosomal gel was carried out by using diffusion cell through membrane as a dialysis membrane. Diffusion cell with inner diameter 24mm was used for the study. 1 mL formulation was placed in donor compartment and freshly prepared 7.4 phosphate buffer was placed in receptor compartment. Dialysis membrane was mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that the membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1mL of sample was withdrawn from receiver compartment after 1, 2, 3, 4, 5, 6, 8,10 & 12 hrs and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10mL in a volumetric flask with distilled water and analysed by UV spectrophotometer.



Drug release kinetics

The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Korsmeyer Peppas model (equation 4).

i) Zero order kinetics:

$R = K_o t$ -- (1)

R=cumulative percent drug

Ko=zero order rate constant

ii) First order kinetics

$\log C = \log Co - K_1 t / 2.303$ -- (2)

where C = cumulative percent drug

K_1 = first order rate constant

iii) Higuchi model

$R = K_H t^{0.5}$ -- (3)

Where R = cumulative percent drug

K_H = higuchi model rate constant

iv) Korsmeyer peppas model:

$M t / M \alpha = K_k t^n$

$\log M t / M \alpha = \log K_k + n \log t$ -- (4)

where K_k = korsermeyer peppas rate constant

'M t / M α' is the fractional drug , n = diffusional exponent, which characterizes the mechanism of drug.

The obtained regression co-efficient (which neared 0.999) was used to understand the pattern of the drug from the Transferosomal gel.

Stability studies

The main objective of the stability testing is to provide evidence on how the quality of the drug product varies with time under the influence of temperature and humidity. The stability study for the Transferosomal gel formulation was done as per ICH guidelines in a stability chamber for a period of 3 months.

RESULTS AND DISCUSSION:

Particle size Analysis

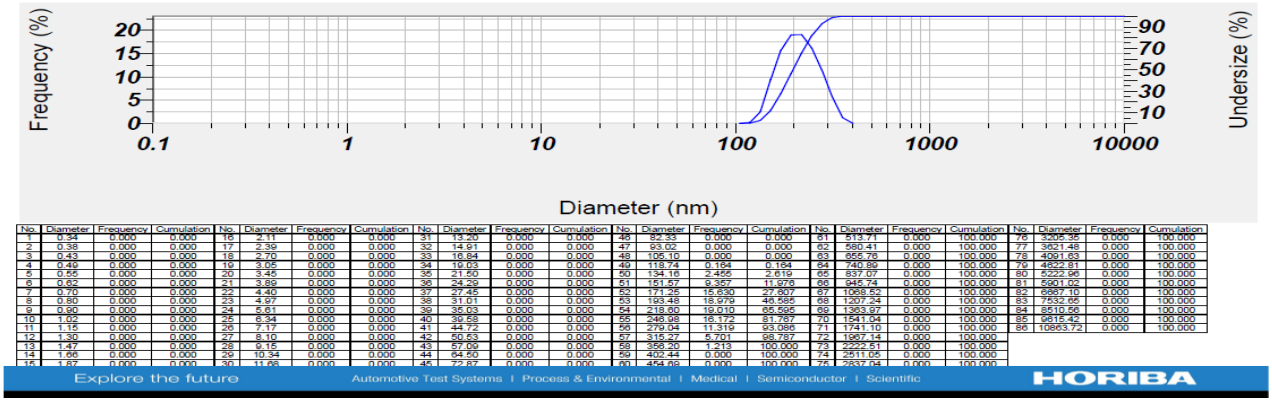


Fig-1: Particle size Analysis of Transferosomes

Zeta potential

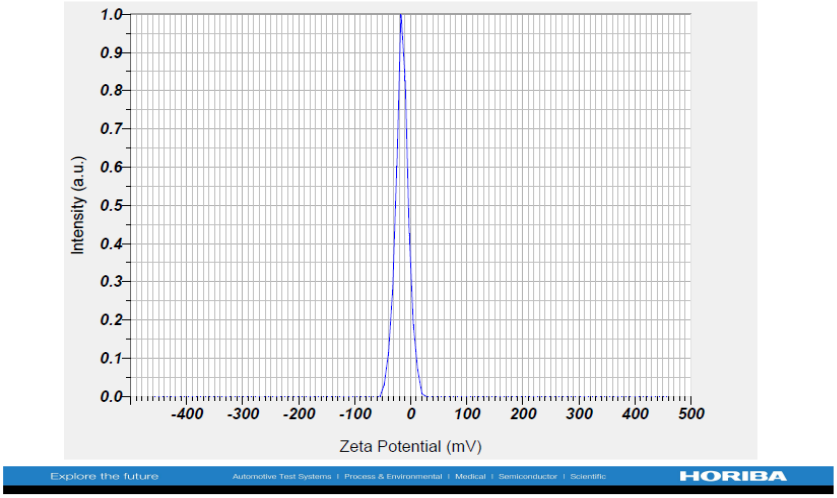


Fig-2: Zeta potential of Transferosomes

Table-3: Evaluation Studies of particle size and Zeta potential Transferosomes

F. No	Particle size (nm)	Zeta potential(mV)
F1	220	-22
F2	198	-24
F3	193	-26
F4	242	-25
F5	172	-33
F6	189	-30
F7	275	-29
F8	233	-23

SEM Analysis

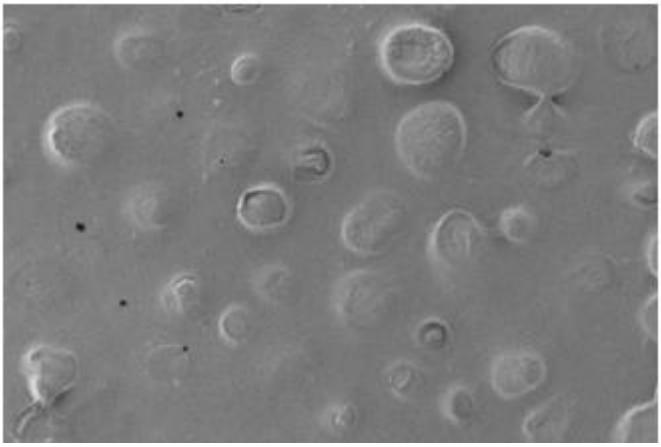


Fig-3: SEM analysis of transferosomes

Yield of Transferosomes

Table-4: Yield of Transferosomes

F. No	Yield (%)
F1	82.5
F2	83.9
F3	79.8
F4	83.5
F5	91.2
F6	89.8
F7	87.5
F8	86.9

Entrapment Efficiency:

Table-5: Drug entrapment efficiency

F. code	Drug entrapment efficiency
F1	82.69
F2	90.15
F3	92.38
F4	86.95
F5	93.87
F6	89.58
F7	92.20
F8	91.93

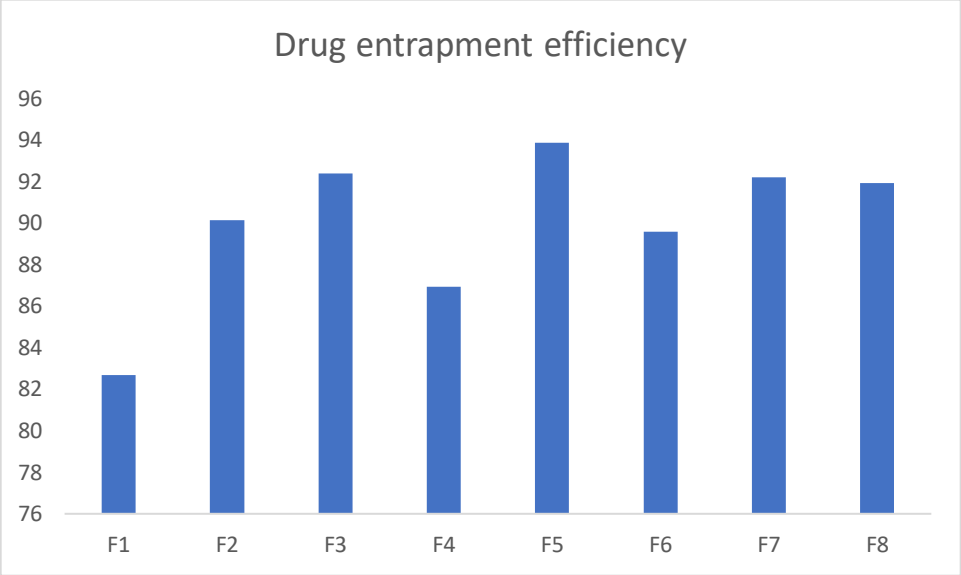


Fig-4: Drug entrapment efficiency of all formulation

Discussion:

The particle size of the transferosomes ranged from 172 to 275 nm. Formulation F5 showed the smallest particle size of 172 nm, whereas F7 exhibited the largest particle size of 275 nm. F1, F2, F3, F4, F6 and F8 showed particle sizes of 220, 198, 193, 242, 189 and 233 nm, respectively. The relatively small vesicle size obtained for most formulations indicates the suitability of the transferosomal system for topical/transdermal delivery of upadacitinib. Smaller vesicles may provide a greater surface area and can facilitate close contact with the skin surface, thereby supporting improved drug deposition and permeation.

The zeta potential values ranged from −22 to −33 mV. F5 exhibited the highest negative zeta potential (−33 mV), while F1 showed the lowest negative value (−22 mV). The negative surface charge provides electrostatic repulsion between vesicles, which helps minimize aggregation and contributes to physical stability of the dispersion. The comparatively higher magnitude of zeta potential observed for F5 suggests better colloidal stability among the formulations.

The SEM analysis demonstrated the formation of discrete transferosomal vesicles with a relatively uniform vesicular structure. The absence of major aggregation and the formation of well-defined vesicles support the particle-size results obtained by particle-size analysis. The morphological characteristics indicate successful formation of the upadacitinib-loaded transferosomal system.

The percentage yield of the formulations ranged from 79.8% to 91.2%. F5 showed the highest yield (91.2%), followed by F6 (89.8%) and F7 (87.5%), while F3 showed the lowest yield (79.8%). The relatively high percentage yield observed for most formulations indicates efficient recovery of the transferosomal vesicles during preparation.

The entrapment efficiency ranged from 82.69% to 93.87%. F5 demonstrated the highest drug entrapment efficiency (93.87%), followed by F3 (92.38%), F7 (92.20%) and F8 (91.93%). F1 showed the lowest entrapment efficiency (82.69%). The high entrapment efficiency indicates that the transferosomal vesicles were capable of efficiently incorporating upadacitinib within their vesicular structure. Differences in entrapment may be attributed to variations in lipid concentration, surfactant composition, vesicle packing, and drug–excipient interactions.

EVALUATION PARAMETERS:

P^H and Viscosity

Table-6: PH and Viscosity values of all formulations

F. code	pH	Viscosity (cps)
F1	6.3	8459
F2	6.5	8796
F3	6.7	9125
F4	6.6	9563
F5	6.2	10250
F6	6.9	11253
F7	6.7	9867
F8	6.4	10230

Spread ability

Table-7: Spread ability values of all formulations

F. code	Spread ability (g.cm/sec)
F1	7.12
F2	7.22
F3	7.45
F4	7.36
F5	7.83
F6	8.20
F7	7.63
F8	7.78

Discussion

The spreadability values of the transferosomal gel formulations ranged from 7.12 to 8.20 g·cm/sec. F1 showed the lowest spreadability (7.12 g·cm/sec), whereas F6 demonstrated the highest spreadability (8.20 g·cm/sec). The results indicate that all formulations possessed satisfactory spreading characteristics.

Good spreadability is an important property of topical gels because it facilitates uniform application over the skin and ensures adequate contact between the formulation and the application site. The higher spreadability of F6 may be associated with its suitable rheological characteristics, allowing the gel to spread easily without excessive resistance. Thus, F6 exhibited favorable spreadability characteristics for topical application.

***In vitro* release study:**

Table-8: *In vitro* drug release profiles of Transferosomal gel (F1-F8)

Time (hr)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	18.76	19.25	17.46	19.82	20.16	21.19	17.48	17.49
2	28.94	27.48	25.83	26.37	30.49	32.46	29.58	25.37
3	48.10	46.37	45.12	46.89	47.86	49.83	45.67	46.89
4	55.69	56.91	51.27	50.27	52.36	59.81	55.48	56.73
6	66.38	67.82	65.72	68.71	68.89	69.83	68.73	65.87
8	77.81	78.85	75.59	73.16	75.98	79.82	75.91	76.19
10	85.92	83.29	80.13	84.56	86.39	88.90	85.92	83.25
12	95.83	93.47	94.86	96.38	97.42	98.73	97.85	95.58

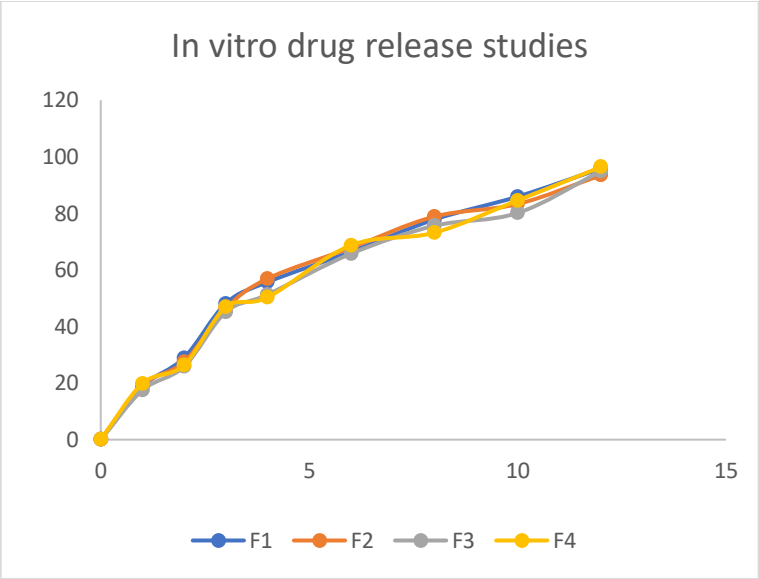


Fig-5: In vitro drug release studies of F1-F4 formulations

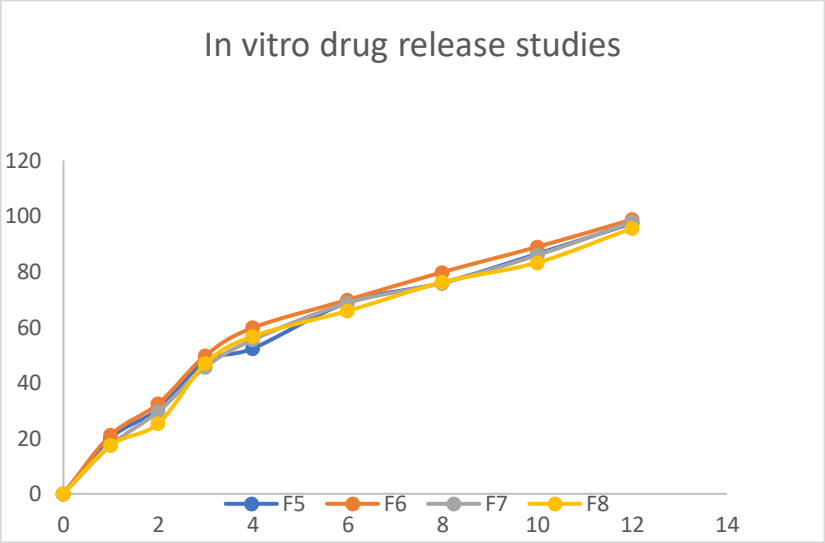


Fig-6: In vitro drug release studies of F5-F8 formulations

Discussion:

The in vitro drug release study of the transferosomal gel formulations was performed in phosphate buffer pH 7.4 for 12 hours. All formulations demonstrated a progressive and sustained release of Upadacitinib throughout the study period.

At 12 hours, the cumulative drug release from F1–F8 was 95.83%, 93.47%, 94.86%, 96.38%, 97.42%, 98.73%, 97.85%, and 95.58%, respectively. Among all formulations, F6 exhibited the highest drug release of 98.73% at 12 hours, while F2 showed the lowest release of 93.47%. The release profile demonstrated an initial drug release followed by a gradual and sustained release over the remaining period.

The relatively prolonged release may be attributed to the incorporation of Upadacitinib into the transferosomal vesicles and its subsequent diffusion from the vesicular lipid structure and gel matrix. The higher release observed with F6 may be associated with its favorable vesicle characteristics, including particle size, zeta potential, and high drug entrapment efficiency. The sustained release behaviour of the transferosomal gel may be advantageous for maintaining drug availability at the topical site and potentially reducing the frequency of application.

Kinetic modelling of drug release

Zero order kinetics

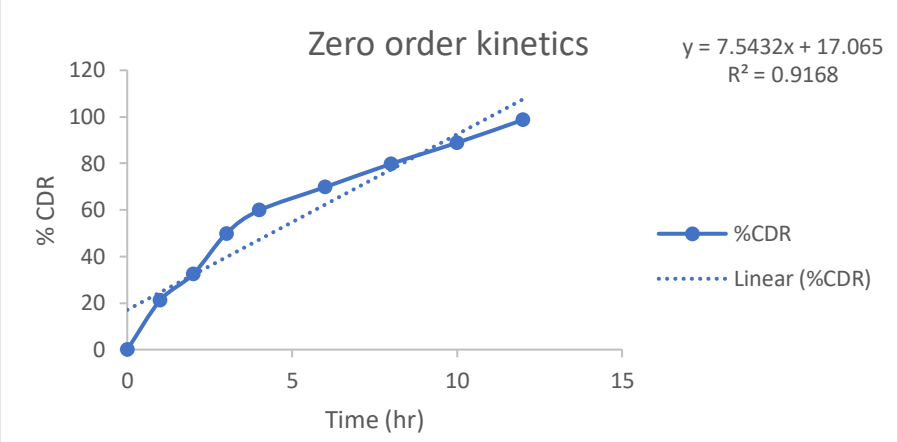


Fig-7: Zero order kinetics of optimized formulation

First order kinetics

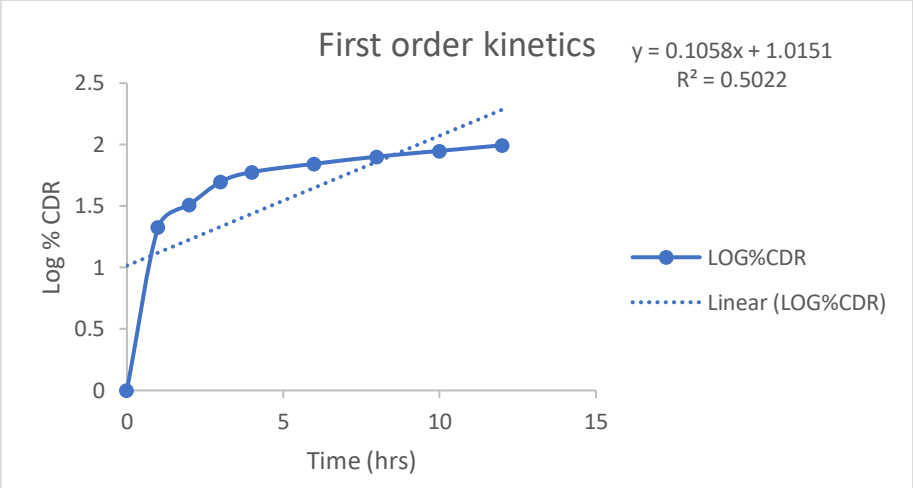


Fig-8: First order kinetics of optimized formulation

Higuchi model

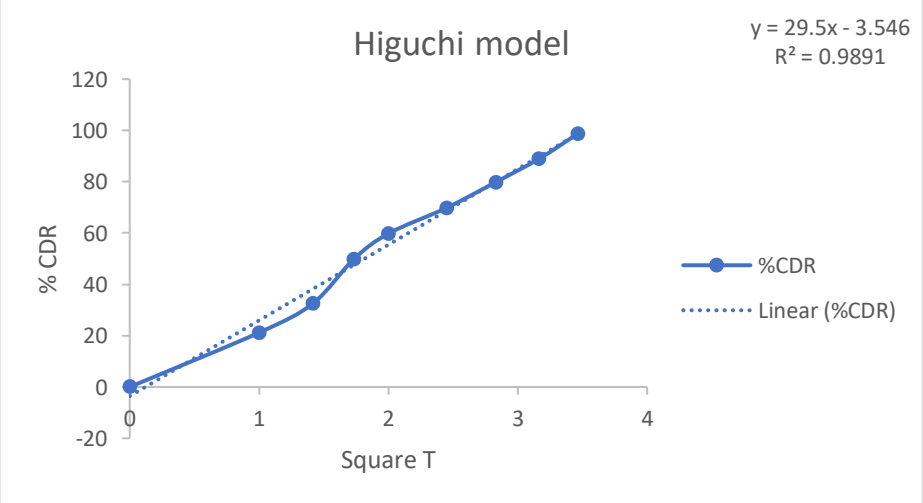


Fig-9: Higuchi model of optimized formulation

Korsmeyer peppas

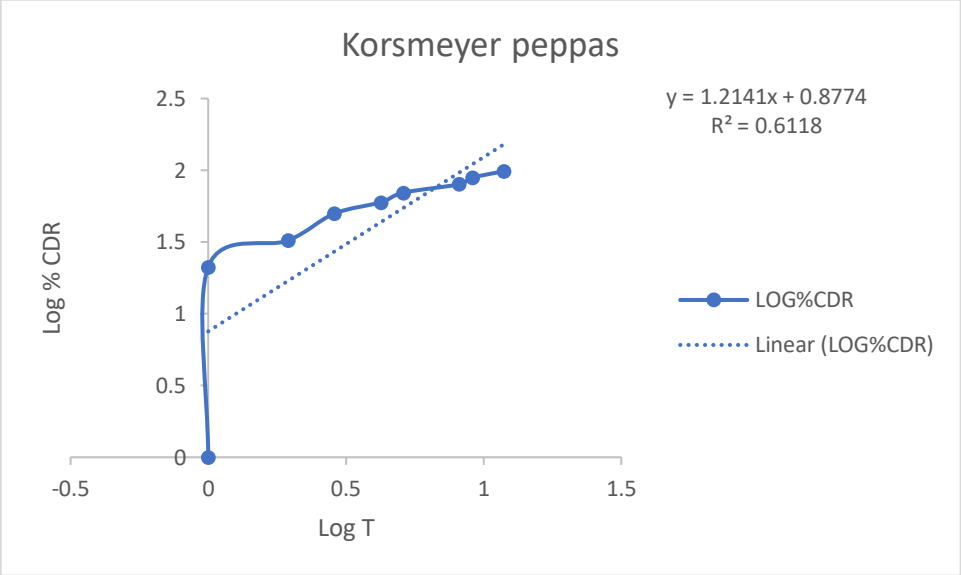


Fig-10: Korsmeyer peppas of optimized formulation

The kinetic values obtained for formulation F6 were shown. The values of in vitro release were attempted to fit into various mathematical models.
Regression values are higher with First order release kinetics. Therefore, Upadacitinib optimized formulation follows Higuchi model release mechanism.

Discussion:

The release data of optimized formulation F6 were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the probable drug-release mechanism. The regression coefficients obtained were 0.916 for zero-order, 0.502 for first-order, 0.989 for Higuchi, and 0.611 for Korsmeyer–Peppas.

Among the evaluated models, the Higuchi model exhibited the highest regression coefficient (R^2 = 0.989). Therefore, the release of Upadacitinib from formulation F6 was best described by the Higuchi model, indicating that diffusion is the predominant mechanism governing drug release from the transferosomal gel. The relatively lower regression coefficient obtained for the Korsmeyer–Peppas model (R^2 = 0.611) further supports that the release behavior was not predominantly governed by a single anomalous transport mechanism.

Thus, the optimized F6 formulation exhibited a diffusion-controlled release pattern, which may contribute to the sustained delivery of Upadacitinib from the transferosomal gel.

Stability studies

Table-9: Stability studies of all formulations

	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	**25^{0}C/60%RH % Release**	98.73	97.81	96.37	95.72	**Not less than 85 %**
F-6	**30^{0}C/75% RH % Release**	98.73	97.50	96.19	95.10	**Not less than 85 %**
F-6	**40^{0}C/75% RH % Release**	98.73	97.15	96.38	95.02	**Not less than 85 %**

DISCUSSION:

Stability studies of the optimized formulation F6 were conducted under different storage conditions for three months, namely 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH. The percentage drug release was monitored at the initial stage and after 1, 2, and 3 months. At 25°C/60% RH, the drug release decreased slightly from 98.73% initially to 95.72% after three months. At 30°C/75% RH, the release decreased from 98.73% to 95.10%, while at 40°C/75% RH, it decreased to 95.02% after three months.

Although a slight reduction in drug release was observed with increasing storage time and temperature, all values remained well above the specified limit of not less than 85%. The relatively small change in drug release indicates that the optimized transferosomal gel maintained satisfactory performance during the three-month stability period. The formulation therefore demonstrated good stability with no major deterioration in drug-release characteristics under the investigated storage conditions.

CONCLUSION:

The study successfully demonstrated the feasibility of developing an Upadacitinib-loaded transferosomal gel using the thin-film hydration technique. The transferosomal system provided desirable vesicle characteristics, good drug entrapment, satisfactory physical stability, and suitable topical gel properties. The optimized F6 formulation exhibited 93.58% drug entrapment efficiency, 89.8% percentage yield, 8.20 g·cm/sec spreadability, and 98.73% cumulative drug release at 12 hours. The sustained release observed from the optimized formulation indicates that incorporation of Upadacitinib into deformable transferosomal vesicles followed by incorporation into Carbopol 934 gel can provide prolonged drug availability at the topical site. The negative zeta potential and smooth, spherical morphology further support the physical stability of the vesicular system. Three-month stability studies demonstrated that F6 maintained satisfactory drug-release performance under the investigated storage conditions, with drug release remaining above 95% after three months. Therefore, based on the in-vitro formulation characteristics and stability findings, Upadacitinib transferosomal gel appears to be a promising approach for enhanced topical delivery and sustained drug release.

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