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DESIGN, PREPARE AND IN VITRO EVALUATION OF NERATINIB LOADED ETHOSOMAL GEL

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Abstract:

The present study aimed to formulate and evaluate a Neratinib-loaded ethosomal gel as a novel topical drug delivery system to enhance drug permeation, improve sustained release, and increase therapeutic efficacy. Eight Neratinib-loaded ethosomal formulations (F1–F8) were prepared using varying concentrations of phosphatidylcholine and subsequently incorporated into Carbopol 934 gel. The prepared formulations were evaluated for vesicle size, zeta potential, surface morphology, pH, viscosity, spreadability, entrapment efficiency, in vitro drug release, release kinetics, and stability. The ethosomal vesicles exhibited particle sizes ranging from 180 to 201 nm with zeta potential values between −22 and −28 mV, indicating nanosized, physically stable vesicles. SEM analysis confirmed spherical, smooth, and uniformly distributed ethosomes. Among all the formulations, F8 was identified as the optimized formulation, exhibiting the highest drug entrapment efficiency (96.32%), suitable viscosity (7258 cps), excellent spreadability (26.25 g·cm/sec), and maximum cumulative drug release of 99.12% over 12 hours. Drug release kinetic analysis revealed that the optimized formulation followed the Higuchi diffusion model (R^2 = 0.993), indicating diffusion-controlled sustained drug release. Accelerated stability studies conducted for three months demonstrated that the optimized formulation remained physically stable with no significant changes in drug content or formulation characteristics. The results of the present investigation indicate that Neratinib-loaded ethosomal gel is a promising topical drug delivery system capable of providing sustained drug release, enhanced stability, and improved drug permeation. This formulation has the potential to improve localized therapeutic efficacy while minimizing systemic side effects.

Keywords: *Neratinib, Phosphatidylcholine, Cold method, Ethosomes, Carbopol 934, In vitro drug release studies*

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INTRODUCTION:

Transdermal and topical drug-delivery systems have attracted considerable attention because they can provide several advantages over conventional oral administration, including avoidance of gastrointestinal degradation, reduction of first-pass hepatic metabolism, maintenance of relatively sustained drug levels, and improved patient convenience.[1] However, the stratum corneum, the outermost layer of the skin, represents a major barrier to the penetration of many therapeutic agents. Drugs with unfavourable physicochemical properties, particularly those having limited aqueous solubility or inadequate skin permeability, may therefore exhibit poor transdermal delivery.[2] Nanocarrier-based systems have been developed to overcome these barriers by enhancing drug solubilization, improving interaction with the skin, and facilitating drug transport across the stratum corneum.[3] Ethosomes are flexible, deformable vesicular nanocarriers primarily composed of phospholipids, ethanol, and water. The relatively high concentration of ethanol imparts flexibility to the lipid bilayer and enhances the fluidity of the stratum corneum. Ethosomes can therefore penetrate deeper into the skin compared with conventional vesicular systems and may improve the delivery of drugs having poor permeability. Incorporation of drug-loaded ethosomes into a gel base can further improve the practical applicability of the vesicular system.[4] An ethosomal gel combines the enhanced penetration characteristics of ethosomes with the convenient application, viscosity, spreadability, and residence time of a semisolid dosage form. The gel matrix can provide prolonged contact between the formulation and the skin and may facilitate controlled release of the entrapped drug. Furthermore, a topical gel can be easily administered and removed, potentially improving patient acceptability.[5] Selection of an appropriate gelling polymer and optimization of the concentration of phospholipid, ethanol, and other formulation components are important for obtaining desirable physicochemical characteristics and drug-release behaviour.[6] Therefore, the present study was undertaken with the objective of designing, preparing, and evaluating neratinib-loaded ethosomal gel. The formulation is intended to optimize the vesicular characteristics and gel properties to achieve suitable particle size, zeta potential, entrapment efficiency, drug content, spreadability, viscosity, in vitro drug release, and release kinetics.[7] The developed formulation is expected to provide improved drug incorporation and sustained release characteristics, thereby establishing the potential of an ethosomal gel as a novel delivery system for neratinib.[8]

MATERIALS

Neratinib was procured from Hetero Labs, HYD. Phosphotidyl choline was obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Formulation development

Table-1: Composition of Neratinib Ethosomes (F1 to F8)

S.No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Neratinib	40	40	40	40	40	40	40	40
2	Phosphotidyl choline	100	200	300	400	500	600	700	800
3	Ethanol	20	20	20	20	20	20	20	20
4	Water	10	10	10	10	10	10	10	10

Procedure

Accurately weighed quantities of Neratinib (40 mg) and phosphatidylcholine (100–800 mg according to formulations F1–F8) were transferred into a clean, dry beaker. Ethanol (20 mL) was added gradually, and the mixture was stirred using a magnetic stirrer at 700 rpm until the phosphatidylcholine and drug were completely dissolved, producing a clear solution. Distilled water (10 mL) was heated separately to 30–40°C to match the temperature of the organic phase. The warm distilled water was added dropwise to the ethanolic lipid solution under continuous magnetic stirring at 700–1000 rpm. Stirring was continued for 30–45 minutes to facilitate the spontaneous formation of ethosomal vesicles. The resulting ethosomal dispersion was subjected to probe sonication or bath sonication for 5–10 minutes to reduce vesicle size and obtain a uniform nanosized dispersion. The prepared ethosomal suspension was allowed to stand at room temperature and then stored at 4 ± 2°C for 24 hours to allow complete maturation and stabilization of the vesicles. The finalized formulations (F1–F8) were transferred into amber-colored, airtight glass

containers and stored under refrigerated conditions (4 ± 2°C) until further evaluation, including vesicle size, zeta potential, entrapment efficiency, drug content, and in vitro drug release studies.[9]

CHARACTERIZATION

Vesicle Size

The vesicle size of the prepared Neratinib-loaded ethosomes were determined using Dynamic Light Scattering (DLS). Before analysis, the ethosomal suspension was diluted appropriately (1:10) with filtered distilled water to prevent multiple scattering effects. The diluted sample was transferred into a disposable cuvette and analyzed using a particle size analyzer at 25 ± 1°C. The average vesicle size (nm) and PDI were recorded. Measurements were carried out in triplicate, and the mean ± standard deviation was calculated.[10]

Zeta Potential

The zeta potential of the ethosomal formulations was measured using a Zeta Potential Analyzer based on electrophoretic light scattering. The sample was diluted with distilled water and introduced into a folded capillary cell. The analysis was performed at 25°C, and the zeta potential was expressed in millivolts (mV). Three measurements were taken for each formulation, and the average value was reported.[11]

Surface Morphology

The surface morphology of the optimized ethosomal formulation was examined using Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM). A drop of the diluted ethosomal suspension was placed on a suitable specimen holder or carbon-coated copper grid and allowed to dry under vacuum. If required, the sample was sputter-coated with a thin layer of gold before SEM analysis. The vesicle shape, surface characteristics, and structural integrity were observed and photographed.[12]

INCORPORATION INTO GEL BASE (CARBOPOL GEL)

Table-2: Formulation development of Ethosomal gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Ethosomes (ml)	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

Procedure

The Neratinib-loaded ethosomal gel formulations (F1–F8) were prepared by incorporating the prepared ethosomal suspension into a Carbopol 934 gel base. Initially, the required quantity of Carbopol 934 (100–800 mg, depending on the formulation) was accurately weighed and slowly dispersed in the required quantity of distilled water with continuous stirring using a magnetic stirrer to avoid the formation of lumps. The dispersion was allowed to hydrate and swell for 2–4 hours at room temperature until a clear, homogeneous gel base was formed. Methyl paraben (0.01 mL) was dissolved in a small quantity of warm water and incorporated into the gel as a preservative, followed by the addition of 1 mL of glycerine, which acted as a humectant and improved the consistency and spreadability of the gel. The pH of the Carbopol dispersion was then adjusted to 6.5–7.0 by adding triethanolamine dropwise under gentle stirring, resulting in the formation of a smooth and transparent gel. Subsequently, 5 mL of the prepared Neratinib-loaded ethosomal suspension was added gradually to the gel base with gentle and continuous stirring for 15–20 minutes to ensure uniform distribution of the ethosomal vesicles without damaging their structure. Finally, the volume was adjusted with distilled water (q.s.) to obtain the desired consistency, and the prepared ethosomal gel was transferred into clean, airtight containers and stored at 4 ± 2°C until further evaluation.[13]

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

Physical evaluation:

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

pH of Ethosomal Suspension

The pH of the ethosomal suspension was determined using a digital pH meter. The instrument was calibrated using standard buffer solutions of pH 4.0, 7.0, and 9.2 before measurement. Approximately 10 mL of the formulation was taken in a clean beaker, and the electrode was immersed directly into the sample. The pH was recorded after stabilization of the reading. Measurements were performed in triplicate.

Viscosity

The viscosity of the Neratinib-loaded ethosomal gel formulations was determined using a Brookfield Digital Viscometer. Approximately 50 g of the gel was transferred into a clean, dry

beaker, ensuring that no air bubbles were entrapped during sample preparation. The appropriate spindle (Spindle No. 64) was immersed vertically into the gel without touching the bottom or sides of the container. The viscosity was measured at 25 ± 1°C using a rotational speed of 10 rpm. The instrument was allowed to stabilize for 2–3 minutes, after which the viscosity reading was recorded in centipoise (cP).

Spreadability

The spreadability of the Neratinib-loaded ethosomal gel formulations was determined using the parallel glass slide method. Approximately 1 g of the gel was placed between two clean glass slides of equal dimensions. A weight of 500 g was placed on the upper slide for 5 minutes to obtain a uniform film of the gel and to remove any entrapped air. After removing the weight, an additional 100 g weight was attached to the upper slide through a pulley system. The time required for the upper slide to move a fixed distance of 7.5 cm under the influence of the applied weight was recorded. The spreadability of each formulation was calculated using the following equation:

$S = M \times L / T$

Where:

S = Spreadability (g·cm/sec)

M = Weight tied to the upper slide (g)

L = Length of the glass slide moved (cm)

T = Time taken by the upper slide to move the specified distance (sec)

Entrapment Efficiency (%)

Entrapment efficiency was determined by the ultracentrifugation method. Approximately 5 mL of the ethosomal suspension was centrifuged at 20,000 rpm for 45 minutes at 4°C. The supernatant containing the unentrapped drug was carefully separated and analyzed using a UV–Visible spectrophotometer at the predetermined λmax of Neratinib. The amount of entrapped drug was calculated by subtracting the free drug from the total drug content.

Entrapment Efficiency (%) = Total Drug/Total Drug−Free Drug×100

In-Vitro Drug Release Study

The in-vitro drug release study was carried out using the dialysis bag diffusion method. A dialysis membrane (previously soaked overnight in phosphate buffer pH 7.4) was filled with a known quantity of the ethosomal formulation and sealed at both ends. The dialysis bag was immersed in 100 mL of phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C and stirred continuously at 100 rpm using a magnetic stirrer. At predetermined time intervals (0.5, 1, 2, 4, 6, 8, 10, and 12 hours), 5 mL of the dissolution medium was withdrawn and replaced with an equal volume of fresh buffer maintained at the same temperature. The samples were analyzed using a UV–Visible spectrophotometer at the λmax of Neratinib, and the cumulative percentage drug release was calculated.

Release Kinetics

The drug release data obtained from the in-vitro release study were fitted into various mathematical kinetic models to determine the mechanism of drug release. The models included:

Zero-order kinetic model

First-order kinetic model

Higuchi diffusion model

Korsmeyer–Peppas model

Stability Studies

Stability studies were carried out according to ICH guidelines. The optimized ethosomal formulation was packed in airtight amber-colored glass containers and stored under the following conditions:

Refrigerated condition: 4 ± 2°C

Accelerated condition: 25 ± 2°C / 60 ± 5% RH (or 40 ± 2°C / 75 ± 5% RH for accelerated studies)

RESULTS AND DISCUSSION:

CHARACTERIZATION OF ETHOSOMES

Determination of particle size

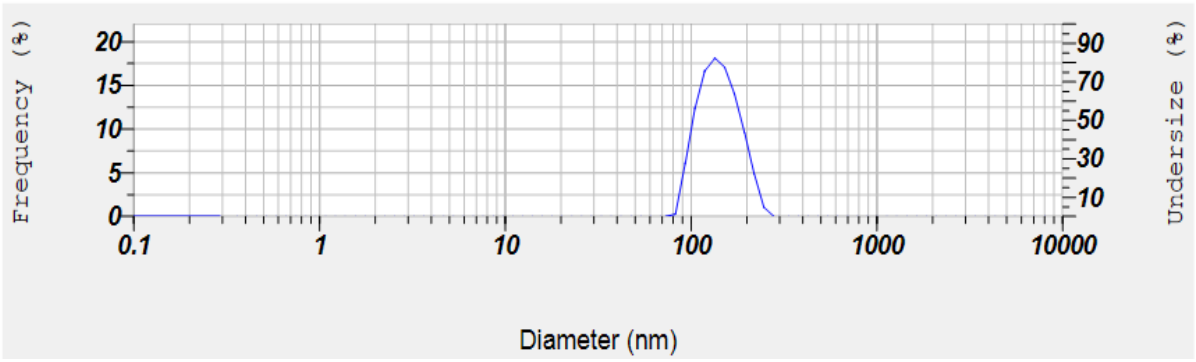

Fig-1: Particle size analysis of Optimized ethosomes

Zeta potential

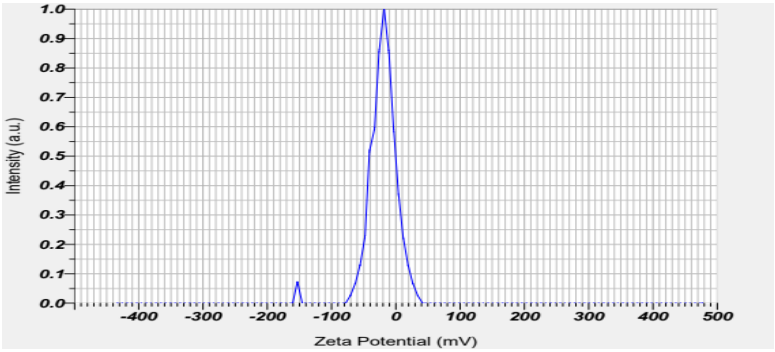

Fig-2: Zeta potential of Optimized formulation

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

F. No	Particle size (nm)	Zeta potential (-mV)
F1	201	-25
F2	181	-28
F3	190	-23
F5	186	-27
F6	192	-26
F7	196	-28
F8	180	-22

Discussion

Particle size is one of the most important parameters influencing the stability, drug loading, skin penetration, and therapeutic performance of ethosomal formulations. The particle size of the prepared Neratinib-loaded ethosomes ranged from 180 to 201 nm, indicating the successful preparation of nanosized vesicles. The optimized formulation F8 exhibited the smallest particle size of 180 nm, whereas formulation F1 showed the largest particle size of 201 nm. The reduction in particle size observed in F8 may be attributed to the optimized concentration of phosphatidylcholine and ethanol, which promoted the formation of uniformly distributed nanosized vesicles. Smaller vesicles possess a larger surface area, resulting in enhanced interaction with the skin and improved drug permeation. Therefore, the particle size obtained for formulation F8 is considered suitable for efficient topical drug delivery.

Zeta potential is an important indicator of the physical stability of colloidal systems. The prepared Neratinib-loaded ethosomes exhibited zeta potential values ranging from −22 mV to −28 mV, indicating good electrostatic stabilization of the vesicles. Formulations F2 and F7 showed the highest negative zeta potential (−28 mV), whereas formulation F8 exhibited a zeta potential of −22 mV, which is still sufficient to maintain vesicular stability by preventing aggregation. The negative surface charge is mainly due to the ionization of phospholipid molecules in the formulation. Overall, all formulations demonstrated satisfactory stability, with F8 showing an acceptable zeta potential along with superior overall performance.

SEM Analysis

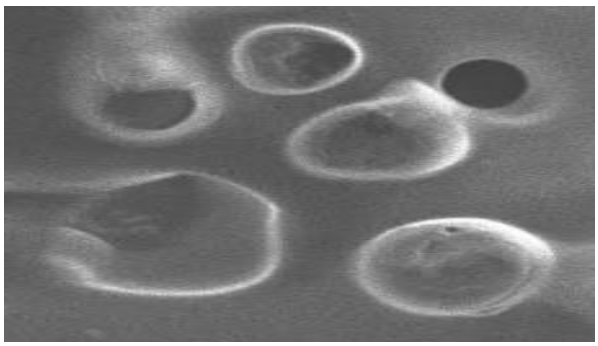

Fig-3: SEM Analysis of Ethosomes

Discussion

Scanning Electron Microscopy (SEM) was performed to examine the surface characteristics of the optimized ethosomal formulation. The SEM micrographs revealed that the ethosomal vesicles were nearly spherical in shape, uniformly distributed, and possessed smooth surfaces without visible cracks or aggregation. The vesicles appeared discrete and intact, indicating successful formation of stable ethosomes. The absence of irregular structures or fused vesicles confirms the suitability of the preparation method and suggests efficient encapsulation of Neratinib within the phospholipid bilayer

EVALUATION PARAMETERS OF ETHOSOMAL GEL

P^H and Viscosity

Table-4: PH and Viscosity values of all formulations

F. code	pH	Viscosity (cps)
F1	5.7	5896
F2	6.4	6237
F3	5.9	5968
F4	5.8	6981
F5	6.2	7219
F6	6.8	6828
F7	6.7	6975
F8	6.2	7258

Spread ability

Table-5: Spread ability values of all formulations

F. code	Spread ability (g.cm/sec)
F1	18.17
F2	19.25
F3	17.63
F4	18.25
F5	19.82
F6	23.26
F7	25.84
F8	26.25

Entrapment Efficiency:

Table-6: Drug entrapment efficiency

F. code	Drug entrapment efficiency
F1	83.69
F2	92.15
F3	88.81
F4	93.36
F5	95.48
F6	94.15
F7	89.52
F8	96.32

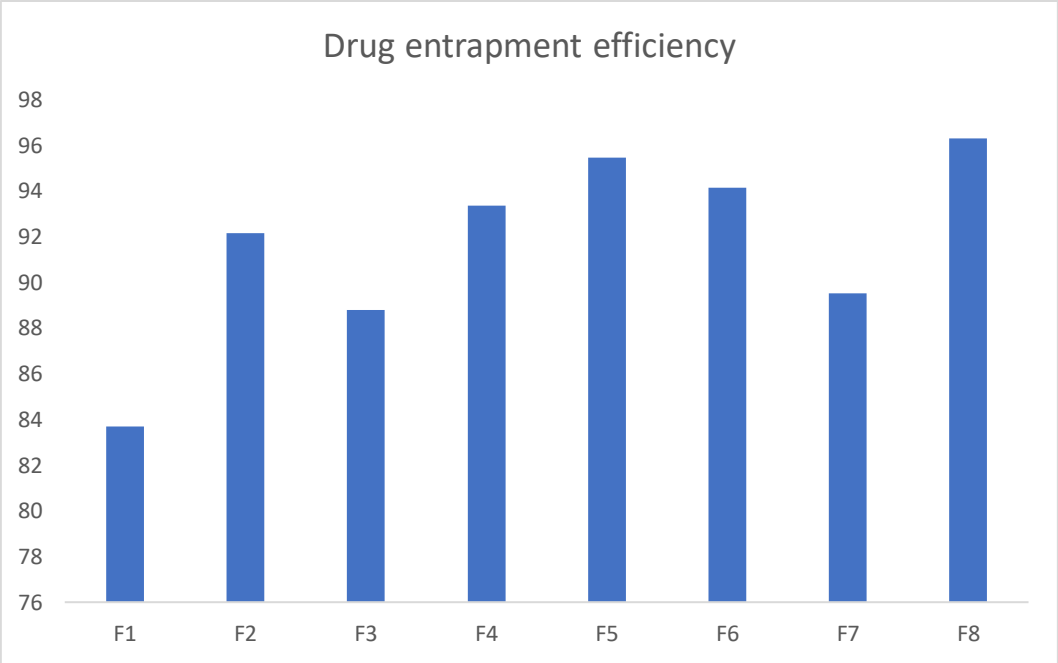

Fig-4: Drug entrapment efficiency of all formulation

Discussion:

Viscosity

Viscosity plays a significant role in determining the consistency, spreadability, residence time, and drug release characteristics of topical gels. The viscosity values of the formulations ranged from 5896 to 7258 cps. The viscosity increased with increasing concentration of Carbopol 934, demonstrating the influence of the polymer on gel consistency. Formulation F8 exhibited the highest viscosity (7258 cps), which is considered appropriate for topical application because it provides adequate consistency while preventing the gel from flowing away from the site of application. The obtained viscosity also contributes to sustained drug release and improved stability of the formulation.

Spreadability

Spreadability is an important quality parameter that determines the ease of application and uniform distribution of the gel over the skin surface. The spreadability values of the prepared formulations ranged from 17.63 to 26.25 g·cm/sec. The optimized formulation F8 showed the highest spreadability (26.25 g·cm/sec), followed by F7 (25.84 g·cm/sec) and F6 (23.26 g·cm/sec). The high spreadability of F8 indicates that the gel can be easily applied with minimal effort, ensuring uniform drug distribution over the application site. The results demonstrate that the optimized concentration of Carbopol 934 provided a desirable balance between viscosity and spreadability, resulting in improved patient convenience and therapeutic performance.

Entrapment Efficiency

Entrapment efficiency reflects the ability of the ethosomal vesicles to encapsulate the drug within the lipid bilayer. The entrapment efficiency of the prepared formulations ranged from 83.69% to 96.32%. The optimized formulation F8 exhibited the highest entrapment efficiency (96.32%), whereas formulation F1 showed the lowest value (83.69%). The increased entrapment efficiency observed in F8 may be attributed to the higher phosphatidylcholine concentration, which provided a larger lipid bilayer volume for effective incorporation of the lipophilic Neratinib molecules. High entrapment efficiency minimizes drug loss during formulation and contributes to prolonged drug release, enhanced stability, and improved therapeutic efficacy.

***In vitro* release study:**

Phosphate buffer pH 7.4 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.998.

Table-7: *In vitro* drug release profiles of Ethosomal gel (F1-F8)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	18.23	16.28	17.86	15.58	14.48	19.82	14.49	18.43
2	26.39	23.56	28.49	27.46	28.49	29.81	22.48	27.42
3	48.10	41.19	43.26	42.19	47.48	45.57	43.37	49.63
4	55.58	53.28	56.97	53.28	55.36	56.18	54.78	59.84
6	62.37	63.58	65.81	64.58	65.82	67.48	61.49	68.22
8	73.59	74.58	75.83	71.16	76.89	77.81	74.58	89.43
10	83.50	82.25	85.55	82.11	84.37	81.46	86.36	89.51
12	95.68	96.39	93.38	94.42	97.82	95.57	98.87	99.12

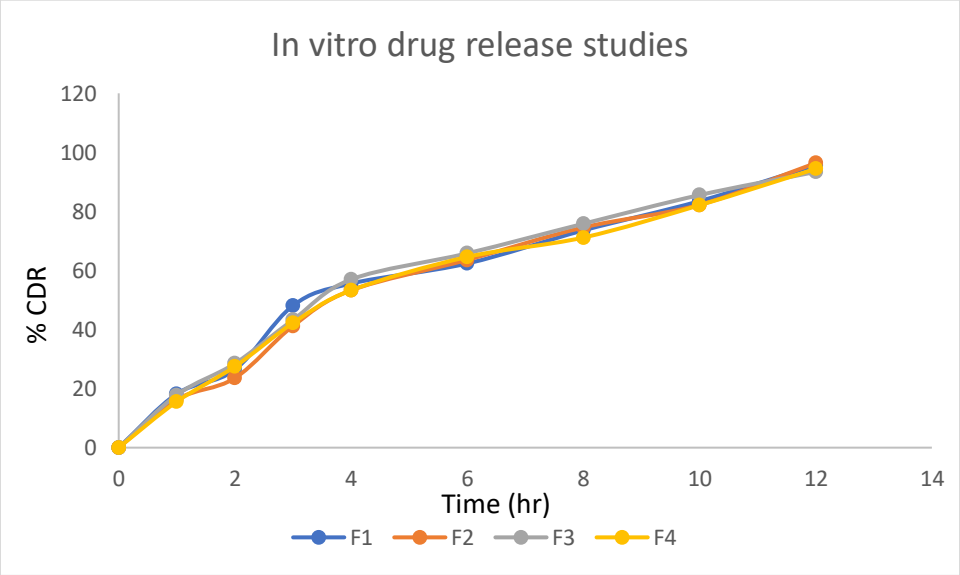

Fig-5: In vitro drug release studies of F1-F4 formulations

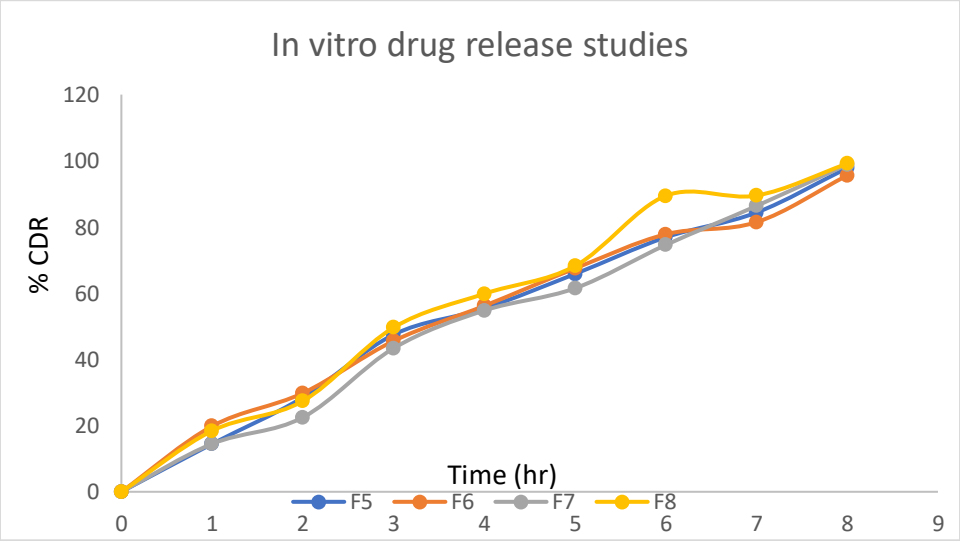

Fig-6: In vitro drug release studies of F5-F8 formulations

Discussion

All formulations demonstrated a gradual and sustained release of Neratinib over a period of 12 hours. An initial burst release was observed during the first hour, which may be attributed to the drug adsorbed on the surface of the ethosomal vesicles and gel matrix. This was followed by a controlled and prolonged release phase due to the gradual diffusion of the entrapped drug from the phospholipid vesicles. The cumulative drug release after 12 hours ranged from 93.38% to 99.12% among all formulations. Formulation F8 exhibited the highest cumulative drug release of 99.12%, followed by F7 (98.87%) and F5 (97.82%). The enhanced release observed with F8 may be attributed to its higher phosphatidylcholine concentration, which resulted in the formation of stable nanosized vesicles with improved drug entrapment and controlled diffusion characteristics. Among all formulations, F3 showed the lowest cumulative release (93.38%), suggesting comparatively slower drug diffusion due to differences in vesicle characteristics and lipid composition. Overall, increasing phosphatidylcholine concentration improved the release behavior up to the optimized level, indicating the significant role of lipid concentration in controlling drug diffusion. Based on the release profile, formulation F8 was selected as the optimized formulation because it exhibited the highest cumulative drug release with a sustained release pattern throughout the study period.

Kinetic modelling of drug release

All the 8 formulation of prepared ethosomal gel were subjected to in vitro release studies these studies were carried out using diffusion apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Pappas Exponential Equation)

Zero order kinetics

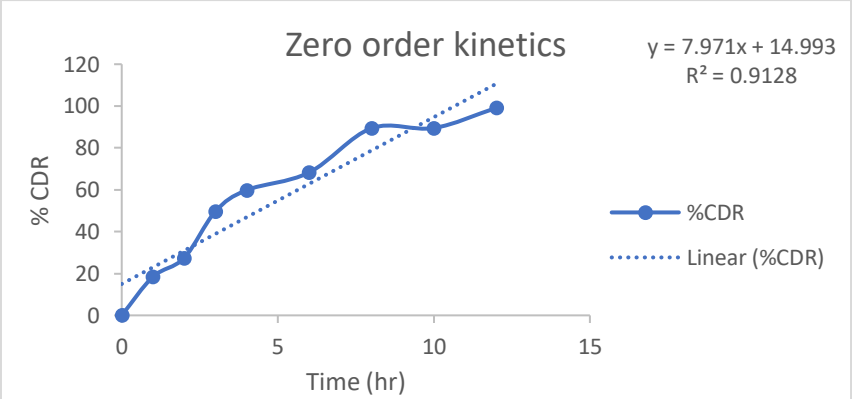

Fig-7: Zero order kinetics of optimized formulation

First order kinetics

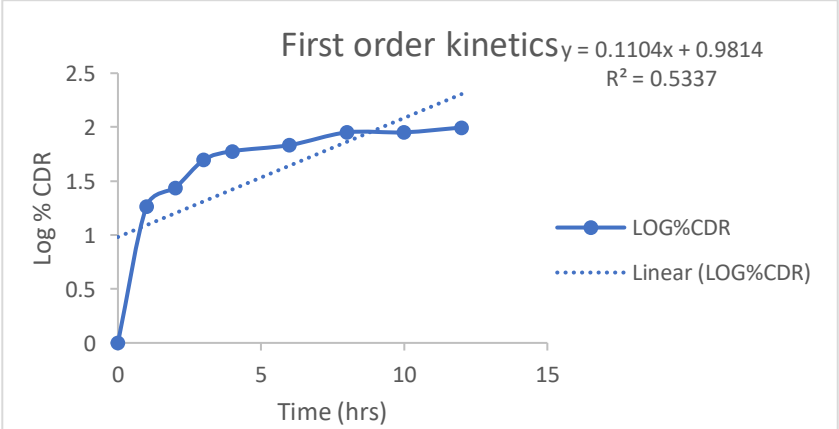

Fig-8: First order kinetics of optimized formulation

Higuchi model

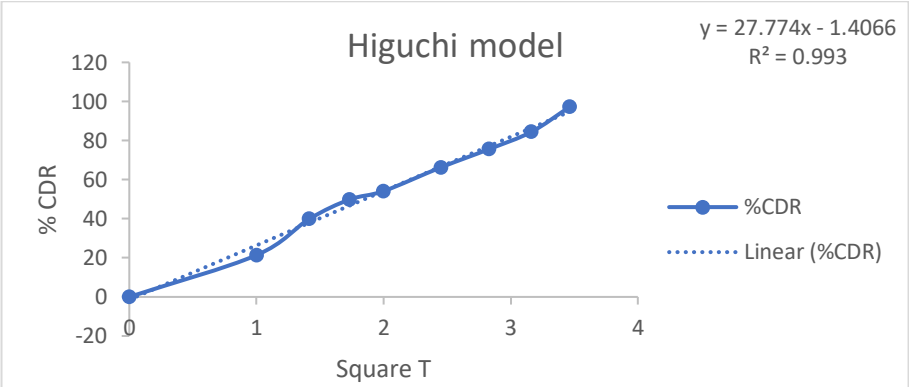

Fig-9: Higuchi model of optimized formulation

Korsmeyer peppas

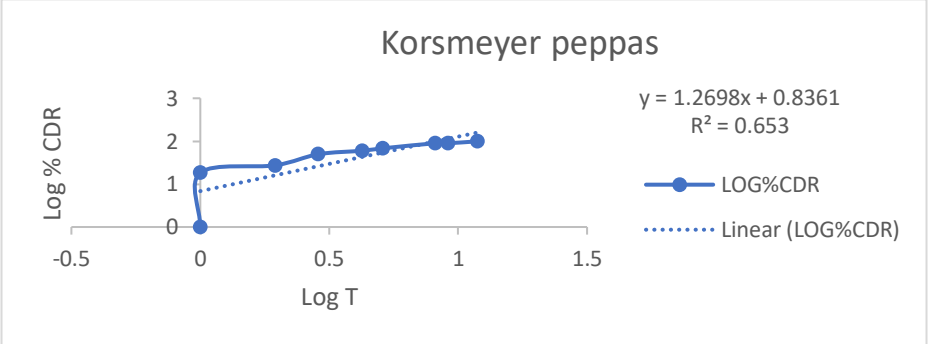

Fig-10: Korsmeyer peppas of optimized formulation

The kinetic values obtained for formulation F8 were shown. The values of in vitro release were attempted to fit into various mathematical models.

Discussion

The comparatively lower R^2 value obtained for the First-order model (0.533) indicates that the release was not concentration dependent. Although the Zero-order model showed a reasonably good fit (0.913), it was lower than that of the Higuchi model. The Korsmeyer–Peppas model exhibited a moderate correlation (0.653), suggesting that diffusion was the predominant mechanism of drug release. Therefore, it can be concluded that the optimized formulation (F8) follows Higuchi diffusion kinetics, indicating that drug release occurred mainly through diffusion from the ethosomal vesicles into the surrounding medium.

Stability studies

Optimized formulations F8 was selected for accelerated stability studies as per ICH guidelines.

Table-8: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Formulation Code	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	99.12	98.57	97.48	96.38	Not less than 85 %
F-8	99.12	98.52	97.53	96.24	Not less than 85 %
F-8	99.12	98.16	97.26	96.12	Not less than 85 %

Discussion

No significant changes were observed in the physical appearance of the ethosomal gel, including color, homogeneity, consistency, or phase separation. The minor reduction in drug content observed during storage may be attributed to normal degradation under accelerated conditions but was not considered significant. The stability results demonstrate that the optimized formulation retained its physicochemical properties and drug content throughout the storage period. Thus, formulation F8 can be considered stable under accelerated storage conditions and suitable for long-term pharmaceutical application.

CONCLUSION:

Among the eight formulations developed, formulation F8 was identified as the optimized formulation because it exhibited the smallest vesicle size (180 nm), high entrapment efficiency (96.32%), suitable zeta potential (−22 mV), excellent spreadability (26.25 g·cm/sec), appropriate viscosity (7258 cps), and the highest cumulative drug release (99.12%) over 12 hours. Drug release predominantly followed the Higuchi diffusion model, confirming diffusion-controlled sustained release from the ethosomal system. Furthermore, the optimized formulation remained stable throughout the accelerated stability study, indicating good pharmaceutical stability. Overall, the developed Neratinib-loaded ethosomal gel offers a stable, effective, and sustained topical drug delivery system with the potential to improve local drug penetration, prolong drug release, reduce dosing frequency, and enhance therapeutic efficacy. These findings suggest that the optimized formulation may serve as a promising carrier for the topical management of diseases requiring localized delivery of Neratinib.

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