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Capecitabine-Loaded Thermoresponsive Nanoemulsion In Situ Gel for Intranasal Delivery in Glioblastoma Therapy

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ABSTRACT

Glioblastoma multiforme (GBM) is an aggressive primary brain tumor with limited therapeutic options, largely due to poor drug penetration across the blood–brain barrier (BBB). Capecitabine, a prodrug of 5-fluorouracil, has demonstrated potential against glioblastoma; however, its short half-life and limited brain delivery may restrict its therapeutic efficacy. This study aimed to develop and evaluate a thermoresponsive intranasal nanoemulsion-based in situ gel of capecitabine for potential nose-to-brain delivery in GBM therapy. Capecitabine-loaded nanoemulsion in situ gels were prepared using triolein, egg lecithin, and Pluronic F127 and F68 by emulsification followed by probe sonication. The formulations were evaluated for physicochemical characteristics, drug content, thermal compatibility, morphology, and in vitro drug release. The optimized formulation (F5) exhibited a gelation temperature of 33.2 ± 0.45 °C and a pH of 6.4, indicating suitability for intranasal administration. F5 showed an average droplet size of 219.7 nm, polydispersity index of 0.12, and zeta potential of -16.6 mV, indicating a uniform and stable nanoemulsion system. The drug content was $97.67 \pm 1.564\%$. Differential scanning calorimetry confirmed compatibility between capecitabine and the formulation excipients, while scanning electron microscopy revealed spherical lipid droplets dispersed within the gel matrix. The optimized formulation demonstrated sustained drug release, achieving $99.64 \pm 0.119\%$ cumulative release over 8 h. Drug release kinetics followed the Higuchi and Korsmeyer–Peppas models, suggesting diffusion-controlled release. Overall, the developed thermoresponsive intranasal nanoemulsion-based in situ gel demonstrates promising physicochemical and drug-release characteristics for potential nose-to-brain delivery of capecitabine in glioblastoma therapy.

Keywords: Nose-to-brain delivery, Nanoemulsion, Thermoresponsive in situ gel, Blood–brain barrier, Brain targeting, Pluronic F127, Sustained drug release

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INTRODUCTION

Glioblastoma (GBM) is the most aggressive and common primary malignant brain tumor in adults, characterized by rapid proliferation, diffuse infiltration into surrounding brain tissue, extensive angiogenesis, and high recurrence rates. Despite multi model treatment involving surgical resection followed by radiotherapy and chemotherapy with temozolamide, the prognosis remains extremely poor, with median survival generally ranging between 12 and 15 months [1-3]. One of the major reasons for treatment failure in GBM is the highly invasive and heterogeneous nature of the tumor. GBM cells infiltrate normal brain parenchyma, making complete surgical removal nearly impossible and contributing to inevitable tumor recurrence. In addition, GBM exhibits significant molecular heterogeneity and rapidly develops resistance to conventional chemotherapeutic agents and radiotherapy [4,5]. critical challenge in GBM therapy is efficient drug delivery to the brain. The presence of the blood–brain barrier (BBB) and blood–brain tumor barrier (BBTB) severely restricts the penetration of therapeutic agents into brain tissue. Tight junctions, efflux transporters such as P-glycoprotein, and enzymatic barriers limit the entry of nearly 98% of small-molecule drugs and almost all macromolecular therapeutics into the central nervous system. Consequently, many promising anticancer agents fail to achieve therapeutic concentrations at the tumor site [6,7]. Although temozolomide remains the current standard chemotherapeutic agent for GBM, its clinical efficacy is limited by systemic toxicity, short drug retention at the tumor site, acquired resistance, and inadequate brain accumulation. Therefore, substantial research efforts are focused on developing advanced drug delivery systems capable of bypassing or overcoming the BBB while improving tumor-specific drug accumulation [7,8].

Capecitabine is an oral fluoropyrimidine prodrug that is enzymatically converted into its active metabolite, 5-fluorouracil (5-FU), preferentially within tumor tissues through thymidine phosphorylase (TP). Glioblastoma (GBM) tissues have been reported to express elevated levels of TP, suggesting that capecitabine may undergo enhanced intratumoral activation, thereby serving as a potential therapeutic option for GBM management. Several preclinical and clinical investigations have explored the role of capecitabine in GBM therapy. Earlier studies demonstrated that concurrent administration of capecitabine with radiotherapy may improve tumor response due to radiation-induced upregulation of thymidine phosphorylase in glioma tissues. Furthermore, metronomic low-dose capecitabine has shown immunomodulatory effects by reducing myeloid-derived suppressor cells (MDSCs), which contribute to the highly immunosuppressive microenvironment of GBM [9,10]. Recent studies continue to support the potential utility of capecitabine in GBM treatment. A 2025 study demonstrated that Glucose transporter 3 (GLUT3)

overexpression in glioblastoma cells significantly enhanced the intracellular uptake and cytotoxicity of both temozolomide and capecitabine, suggesting that GLUT3 may facilitate capecitabine uptake in GBM cells. The study further showed improved chemosensitivity in xenograft models, suggesting a promising role for capecitabine-based combination therapy in glioblastoma [11,12].

Despite these encouraging findings, several challenges still limit the clinical effectiveness of capecitabine in GBM. The drug exhibits a short elimination half-life and limited penetration across the blood–brain barrier (BBB), which restricts sufficient drug accumulation at the tumor site. Systemic administration may also produce gastrointestinal and hematological adverse effects before adequate concentrations reach brain tissue.

Among emerging approaches, intranasal drug delivery has gained considerable attention as a non-invasive strategy for direct nose-to-brain transport. This route enables drugs to bypass the BBB through olfactory and trigeminal neuronal pathways, thereby enhancing brain bioavailability and reducing systemic adverse effects [13]. Consequently, advanced drug delivery strategies such as nanoparticles, nanoemulsions, liposomes, and intranasal thermoresponsive in situ gels are increasingly being explored to enhance brain targeting, prolong residence time, improve controlled release, and reduce systemic toxicity of capecitabine in glioblastoma therapy [14, 15]. Therefore, the present study aimed to develop and evaluate a thermoresponsive intranasal nanoemulsion-based in situ gel of capecitabine using emulsification technology for potential nose-to-brain delivery. The intranasal route was selected as a non-invasive strategy to bypass the BBB and enhance drug delivery to brain tissue through olfactory and trigeminal pathways. Incorporation of capecitabine within lipid nanodroplets was hypothesized to improve drug localization, prolong nasal residence time, provide sustained drug release, and minimize local tissue irritation. Furthermore, the lipophilic nature of the nanoemulsion may enhance tumor uptake, while elevated thymidine phosphorylase expression in glioblastoma tissues could facilitate the selective conversion of capecitabine to the active metabolite 5-fluorouracil (5-FU), thereby potentially improving therapeutic efficacy and reducing systemic toxicity and first-pass metabolism.

MATERIALS AND METHOD

Materials

Capecitabine, triolein, egg lecithin, Pluronic F68, and Pluronic F127 were purchased from Sigma-Aldrich, India. HPMC K15, sodium metabisulfite, and benzalkonium chloride were purchased from Bharathi Scientific Traders, Medchal, Malkajgiri Dist, Telangana State, India. HPLC-grade water was used for all experiments.

Methods

Establishment of analytical methods for the determination of capecitabine by RP HPLC

Chromatographic conditions

Quantitative determination of capecitabine was performed using a reverse-phase HPLC method adapted from the validated procedure reported by Ravisankar et al. (2013) [16], with minor modifications where required for the present study. Chromatographic separation was achieved using a Shimadzu LC-20AT Prominence HPLC system equipped with a UV detector and a WELCHROM C18 column (250 × 4.6 mm, 5 µm). The optimized chromatographic conditions employed in the present investigation are summarized in Table 1.

Table 1: Optimized chromatographic conditions used for RP-HPLC determination of capecitabine (adapted from Ravisankar et al. 2013).

Parameter	Chromatographic conditions
Instrument	SHIMADZU LC-20AT prominence liquid chromatograph
Column	WELCHROM C18 Column (4.6 mm i.d. X 250mm, 5µm particle size)
Detector	SHIMADZU SPD-20A prominence UV-Vis detector
Diluents	Methanol: Acetonitrile: Water (50:30:20, v/v, pH-4.6 using o-phosphoric acid)
Mobile phase	Methanol: Acetonitrile: Water (50:30:20, v/v, pH-4.6 using o-phosphoric acid)
Column modifier	Triethylamine (0.5 mL)
Flow rate	1mL/min.
Detection wave length	UV at 245 nm.
Run time	5 minutes
Column back pressure	156kgf
Temperature	Ambient temperature(25°C)
Volume of injection loop	20µL
Retention time (tR)	3.45min
Theoretical plates[th.pl] (Efficiency)	10,080
Theoretical plates per meter [t.p/m]	201,597
Tailing factor (asymmetry factor)	1.069

Construction of a calibration curve

Preparation of standard stock solution

Accurately weighed quantity of capecitabine was transferred into a volumetric flask, and the drug was dissolved in HPLC-grade methanol. The remaining volume was brought to the mark with methanol to obtain a capecitabine concentration of 1mg/mL.

Preparation of calibration curve standards

The stock solution was diluted with the mobile phase to obtain a capecitabine concentration of 100 µg/ml. The stock solution was further diluted with the mobile phase to obtain final concentrations of 2, 4, 6, 8, and 10 µg/ml. A 20 µl volume of the calibration curve standard was injected into the HPLC, and the wavelength was determined in spectrum mode. Replicates of each calibration standard solution (2, 4, 6, 8, 10 µg/mL) were injected using a 20 µl fixed loop system, and the chromatograms were recorded. Calibration curves were constructed by plotting the concentration of capecitabine on the X-axis and peak areas of standard capecitabine on the Y-axis, and regression equations were computed for Capecitabine.

Pre-formulation studies

Determination of the solubility of capecitabine in various solvents

Solubility studies of the drug are done in water, Ethanol, Methanol, DMSO, 6.4 pH phosphate buffer solutions, 6.8 pH phosphate buffer solutions, and 7.4 pH phosphate buffer solutions. The drug was added in excess to each solvent. To equilibrate the dissolved and undissolved drug, the samples were placed in a conical flask, mechanically shaken for 1 hour at 37 °C, and then left to equilibrate. A 0.45-micron Whatman filter was used to filter the solutions. The drug concentration in the filtrate was determined after appropriate dilutions by the HPLC method described above.

Formulation development and preparation of capecitabine in situ gel

Rationale for Variable Selection

The formulation variables were selected based on their reported influence on nanoemulsion stability, gelation behavior, particle size distribution, and intranasal retention characteristics. Glyceryl trioleate was selected as the lipid phase owing to its biocompatibility, lipophilic nature, and reported suitability for intranasal administration. Egg lecithin was used as an emulsifying agent to stabilize lipid droplets and improve nanoemulsion formation. Pluronic F127 and Pluronic F68 were selected as thermoresponsive polymers because of their ability to undergo sol-to-gel transition at physiological temperatures and enhance nasal residence time [17-20]

Preparation of lipid phase

The required quantity of lipid (Triolein) was weighed into a beaker. To it, egg lecithin was added and dissolved with the aid of heating at 50°C.

Preparation of the aqueous phase

The required quantity of water was weighed into another beaker, and to it, sodium metabisulfite, pluronic F127, pluronic F68, and benzalkonium chloride were added, and specified quantities of capecitabine were dissolved and kept aside until pluronic F127 and F68 were dissolved in water.

Emulsification of the lipid phase to produce an in-situ gel

The lipid phase was then emulsified using homogenization after reaching to room temperature at 8000 RPM for 15 minutes by slowly adding the aqueous phase. The emulsified mixture was subjected to ultrasonication with a probe sonicator at 80% amplitude for 20 minutes, with 2-second on/off cycles. The overheating produced by the probe sonicator is controlled by keeping the emulsion in an ice bath. The concentrations of lipid and polymers were varied to obtain an optimized formulation with suitable gelation temperature, particle size, drug content, and sustained drug release characteristics by trial and error and the selected compositions were given in Table 2.

Table 2: Compositions of capecitabine in situ forming gels

No. of Formulations	Glyceryl Trioleate(gm)	Egg lecithin(gm)	Pluronic F127 (%)	Pluronic F68 (%)	Capecitabine (gm)	Water
1.	1	0.2	1.5	0.8	0.017	q.s to 10gms
2.	1	0.2	1.6	0.8	0.017	
3.	1	0.2	1.8	0.8	0.017	
4.	1	0.2	1.9	1.0	0.017	
5.	1.5	0.2	2.1	1.0	0.017	
6.	2	0.2	2.1	1.0	0.017	

Optimization of formulations

Preliminary trial formulations were prepared by varying the concentrations of glyceryl trioleate, Pluronic F127, and Pluronic F68 to optimize the physicochemical characteristics of the nanoemulsion in situ gel system. The formulations were evaluated based on gelation temperature, pH, particle size, polydispersity index, zeta potential, drug content, and in vitro drug release profile. Among the prepared formulations, formulation F5 was selected as the optimized formulation due to its desirable gelling temperature close to nasal physiological conditions, a narrow particle-size distribution, satisfactory drug content, and sustained drug-release behavior.

Evaluation of in situ gels

The formulations prepared were subjected to various evaluation parameters such as gelation temperature, pH, viscosity, drug content, drug-entrapped lipid droplet size analysis, distribution, and zeta potential, drug diffusion studies, and scanning electron microscopy.

Gelation temperature

The temperature at which the formulation turns from solution to gel is known as gelation temperature. In order to measure gelation temperature a test tube containing two milli Liters of in situ gel was submerged in a water bath. The water bath temperature was then gradually and steadily raised. After five minutes of gel equilibration at each setting, the formulation was checked for gelation. When tilted to 90°, the meniscus stopped moving & temperature was noted.

pH test

A digital pH meter was used to measure the formulation's pH. A portion of each composition was transferred to a separate beaker and diluted with 25 mL of distilled water. The pH of each formulation was then measured by dipping the pH meter electrode.

Determination of drug content

Methanol was used to dilute the formulation after a quantity was placed in a 10ml volumetric flask. To fully extract capecitabine into the solvent, the volume is brought to 10 ml with the same solvent, sonicated for 5 minutes in an ultrasonic bath, and filtered. This was then degassed and injected into the HPLC for analysis after appropriate dilutions were prepared with the mobile phase. The following formula was used to determine the % drug content.

$$\% \text{ drug content} = \frac{\text{test area} \times \text{standard concentration} \times \text{dilution factor}}{\text{standard area} \times 1000 \times \text{label claim}} \times 100$$

Studies on drug release (*In vitro*)

In vitro drug release studies were performed using a dialysis membrane diffusion technique in order to evaluate the release behavior of capecitabine from the nanoemulsion-based in situ gel system. The dialysis membrane served as a semi-permeable barrier that retained lipid droplets and polymeric components within the dialysis bag while permitting diffusion of the released drug into the external dissolution medium. This method is widely employed for evaluating sustained-release nanoformulations and lipid-based delivery systems (Yu et al. 2019), (ICH guidelines, Q2, 2023). Dialysis membrane (MWCO 12,000–14,000 Da) was soaked overnight in distilled water before use. The formulation was placed in cellulose dialysis tubing. USP dissolution instrument type II (Labindia dissolution tester 8000) with the following parameters depicted in Table 3 below was used to conduct the drug release investigations. The samples were withdrawn at the specified time intervals listed in Table 3, and the HPLC method described above was used to analyze them. To determine the order of drug release, the acquired data were fitted to first- and zero-order equations.

Table 3: Various parameters used for in vitro drug release studies

S.No	Dissolution Parameters	
1	Speed	50 rpm
2	Stirrer	Paddle type
3	Volume of medium	250ml
4	Duration	8 hours
5	Time intervals	10min, 20min, 30min, 45min, 60min, 2 hrs, 4hrs, 6hrs and 8hrs
6	Volume withdrawn	5ml
7	Medium used	6.4 pH phosphate buffer
8	Temperature	37 ⁰ c
9	Dissolution test apparatus	USP type II (Lab india dissolution tester DS8000)

Examination of Particle size and zeta potential

Malvern ZetaSizer was used to measure the average dispersed lipid droplet size and polydispersity index. The uniformity of the drug-entrapped lipid droplet size and their size distribution in the in situ gel are represented by the PDI. The formulation was placed in a cuvette with a dip cell attached, and observations were taken at a light-scattering angle of 90° after it was diluted with HPLC water to achieve an ideal kilo count per second of 50 to 100. During the measurement, the temperature was constant at 25.0 °C. Using the same device and built-in software, the zeta potential was also determined using the Helmholtz-Smoluchowski equation and the electrophoretic mobility of globules.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) analysis was performed to investigate possible interactions between capecitabine and the excipients used in the optimized nanoemulsion in situ gel formulation. Pure capecitabine and the optimized formulation were subjected to DSC analysis using a differential scanning calorimeter (Mettler Toledo, Switzerland) equipped with STARe SW 9.01 software. Accurately weighed samples were sealed in perforated aluminum pans and scanned over a temperature range of 0–300 °C under a nitrogen atmosphere at a constant heating rate of 10 °C/min. Figures 1 and 2 present the thermograms of the pure drug and the optimized formulation, respectively.

Viscosity determination

The rheological properties of in situ gels were studied using a Brookfield LV viscometer. The factors that affect the viscosity of the samples were temperature, pressure, and sample size, so these parameters were kept constant during viscosity measurement. At various locations along the path, the helipath T-bar spindle (SC4-18) was shifted up and down to provide viscosities. And the spindle rpm was slowly increased at different points, then decreased. This gives the viscosity of the formulation at different rpm. Throughout the viscosity measurement, the torque reading was consistently kept above 10%. The viscosity of the in situ gel was determined by averaging three measurements.

Scanning electron microscopic (SEM) studies

The formulated optimized capecitabine in situ gel was visually characterized by scanning electron microscopy. Using this SEM analysis, we can determine the particle shape and external morphology of the sample. For SEM analysis, samples were gold sputter-coated and tested in an argon atmosphere.

Statistical Analysis

All experiments were performed in triplicate, and results were expressed as mean $\pm$ standard deviation (SD). Data analysis was performed using Microsoft Excel, and graphical representations were generated accordingly.

RESULTS AND DISCUSSION

RP-HPLC Method Development and Validation [21]

The RP-HPLC method employed in the present study was adapted from the validated analytical procedure reported by Ravisankar et al. (2013) [16] and demonstrated excellent chromatographic performance under optimized experimental conditions for the quantitative estimation of capecitabine in the developed intranasal nanoemulsion-in-situ gel formulations. The chromatographic conditions produced a sharp, symmetrical peak with a retention time of 3.45 min, indicating satisfactory separation and method specificity. The calibration curve of capecitabine exhibited good linearity over the concentration range of 2–10 $\mu\text{g/mL}$, with a correlation coefficient (r^2) of 0.999, demonstrating the reliability and accuracy of the analytical method for estimating capecitabine in formulation studies. Optimized chromatographic conditions were shown in Table 1.

Solubility Studies of Capecitabine

Solubility studies were performed in various solvents and buffer systems to select a suitable dissolution medium and optimize formulation development. Capecitabine exhibited high solubility in ethanol, methanol, DMSO, and phosphate buffer systems. Among the aqueous buffers, appreciable solubility was observed in pH 6.4 phosphate buffer, which falls within the physiological nasal pH range; therefore, it was selected as the diffusion medium for subsequent in vitro release studies. The results were given in Table 4.

Table 4: Solubility studies of capecitabine in various Solvents

Solvent(pH)	Solubility (mg/ml)
Water	26.24 $\pm$ 0.031
Ethanol	207.32 $\pm$ 0.042
Methanol	46.52 $\pm$ 0.065
DMSO	76.312 $\pm$ 0.076
6.4 pH phosphate buffer solutions	34.38 $\pm$ 0.062
6.8 pH phosphate buffer solutions	39.36 $\pm$ 0.046
7.4 pH phosphate buffer solutions	47.52 $\pm$ 0.086

Optimization of Nanoemulsion In Situ Gel Formulations

Preliminary trial formulations (F1–F6) were prepared by varying the concentrations of glyceryl trioleate, Pluronic F127, and Pluronic F68 to obtain a formulation with suitable physicochemical and release characteristics for intranasal administration. Triolein was selected as the lipid phase

due to its biocompatibility and suitability for intranasal lipid-based delivery systems [22]. Pluronic F127 and F68 undergo temperature-dependent micellar aggregation, resulting in sol-to-gel transition at physiological temperatures [23]. The prepared formulations were evaluated based on gelation temperature, pH, drug content, particle size distribution, and in vitro drug release behaviour. Among the developed formulations, F5 exhibited desirable gelation temperature, acceptable pH, narrow particle size distribution, high drug content, and sustained drug release profile, and was therefore selected as the optimized formulation. The results were depicted in Table 5.

Gelation Temperature and pH

Gelation temperature is an important parameter for thermoresponsive intranasal in situ gels, as the formulation should remain in a liquid state during administration and rapidly convert to a gel at nasal physiological temperature. The gelation temperatures of formulations ranged from 30.3 ± 0.16 °C to 40.5 ± 0.51 °C. An increase in polymer concentration resulted in an increased gelation temperature due to enhanced micellar aggregation and gel network formation (Bahadur et al. 2020b). Formulation F5 exhibited a gelation temperature close to nasal physiological conditions and was considered suitable for intranasal administration. The pH values of all formulations ranged between 6.0 and 6.7, which are within the acceptable nasal pH range and therefore expected to minimize nasal irritation. The results were given in Table 5

Table 5: Gelation temperature and pH for in situ gel formulations

Formulation Code	Gelation Temperature (°C)	pH	% drug content
F1	30.3±0.16	6.5	90.37
F2	31.5±0.11	6.1	92.56
F3	32.1±0.13	6.2	91.32
F4	32.3±0.26	6.0	94.63
F5	33.2±0.45	6.7	97.67
F6	40.5±0.51	6.3	95.12

Drug Content

Drug content analysis was performed to evaluate the uniformity and distribution of capecitabine within the developed nanoemulsion in situ gel formulations. The drug content of all formulations ranged from 90.37% to 97.67%, indicating uniform distribution of capecitabine throughout the formulation. The optimized formulation F5 exhibited maximum drug content, suggesting efficient incorporation of capecitabine within the lipid-polymeric matrix. The data was shown in Table 5

Particle Size Distribution and Zeta Potential Analysis

Particle size distribution and zeta potential are critical parameters that influence the stability, drug-release behavior, and nasal permeation characteristics of nanoemulsion systems. The optimized formulation F5 exhibited an average droplet size of 219.7 nm with a polydispersity index of 0.12, indicating a narrow and uniform droplet size distribution. The small droplet size may facilitate enhanced mucosal permeation and improved nasal absorption [24].

The zeta potential of the optimized formulation was -16.6 mV, indicating moderate electrostatic stability of the nanoemulsion system and a reduced tendency for globule aggregation [25]. The properties of the selected formulation were shown in Table 6.

Table 6: Physicochemical properties of capecitabine intranasal in-situ forming gel (selected formulation F5)

Parameter	Result
Gelation temperature	$33.2 \pm 0.45^\circ\text{C}$
pH	6.4 pH units
Dispersed lipid droplet size	219.7 nm
Poly dispersity index	0.12
Zeta potential	-16.6mv
Percentage drug content	$97.67 \pm 1.564\%$
Viscosity	9.1466 cp

Differential Scanning Calorimetry (DSC) Studies

Differential scanning calorimetry (DSC) studies were performed to investigate the thermal behavior of capecitabine and its compatibility with the excipients used in the nanoemulsion in situ gel formulation. The DSC thermogram of pure capecitabine exhibited a characteristic sharp endothermic peak at approximately 120°C , corresponding to the melting transition of crystalline capecitabine and confirming its crystalline nature.

In the DSC thermogram of the optimized capecitabine-loaded nanoemulsion in situ gel formulation, the characteristic drug peak was retained with slight broadening and reduction in intensity. The reduction in peak intensity may be attributed to molecular dispersion of capecitabine within the lipid-polymeric matrix and partial reduction in crystallinity during formulation development. The absence of any additional peaks or significant peak shifts indicated that no major chemical interaction or incompatibility occurred between capecitabine and the formulation excipients [26]. The DSC thermograms are presented in Figures 1 & 2.

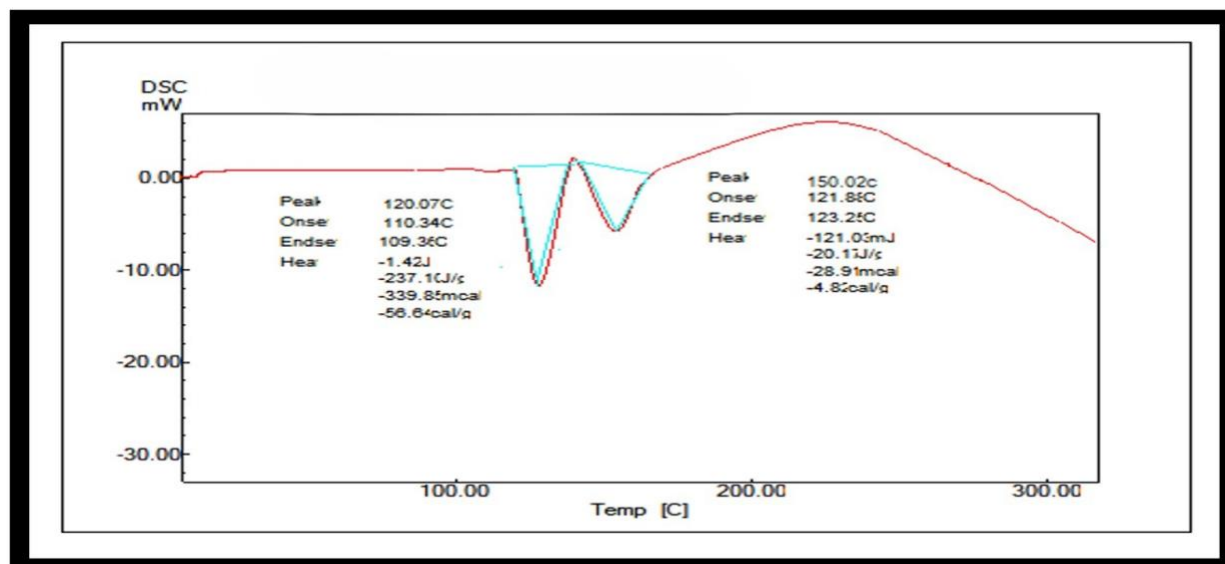


Figure 1 DSC thermogram of pure capecitabine. A characteristic endothermic transition was observed with a peak temperature of approximately 120.07 °C.

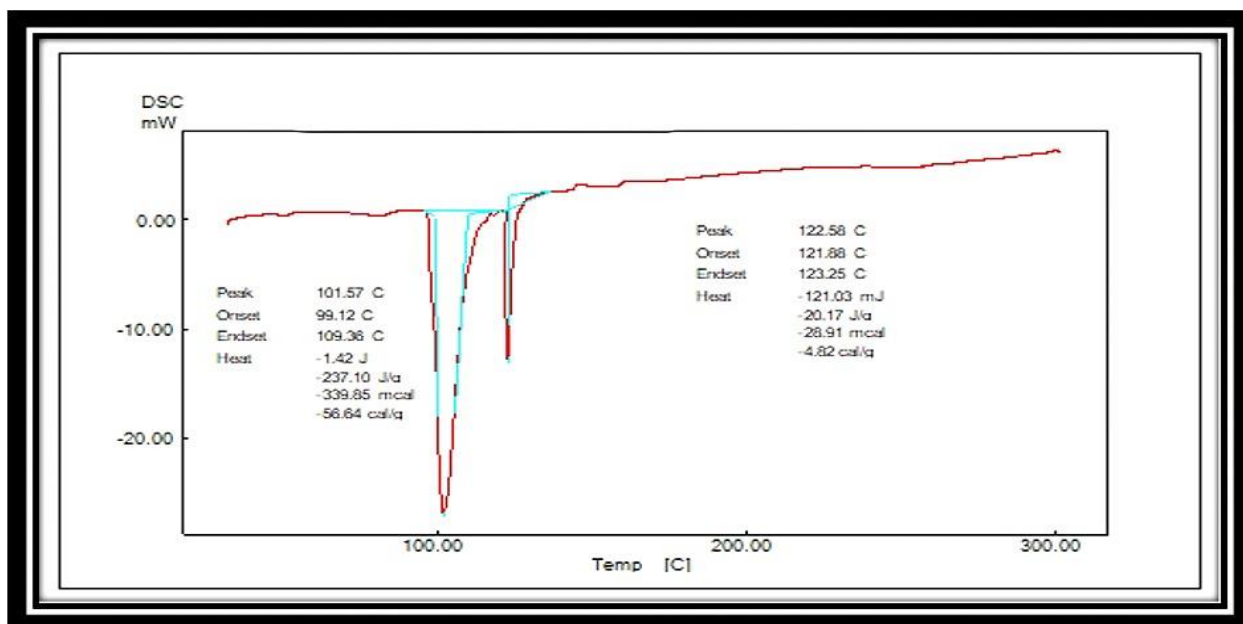


Figure 2 DSC thermogram of the optimized capecitabine-loaded nanoemulsion in situ gel (F5). The thermal profile indicates incorporation of capecitabine within the lipid-polymeric formulation matrix.

These findings suggest successful incorporation of capecitabine into the nanoemulsion in situ gel system while maintaining drug stability throughout the formulation process.

In Vitro Drug Release Studies [27]

In vitro drug release studies were performed using the dialysis membrane diffusion method to evaluate the release characteristics of capecitabine from the nanoemulsion in situ gel formulations. All formulations exhibited sustained drug-release behaviour throughout the study period. An initial

burst release was observed during the early phase, which may be attributed to the fraction of drug present in the aqueous phase of the formulation. Thereafter, drug release occurred gradually from the lipidic and polymeric matrix. The initial release of approximately 30% drug within the first hour may be attributed to the fraction of capecitabine present in the aqueous phase, whereas the sustained release observed thereafter suggests substantial incorporation of the drug within the lipidic and gel matrix system. Although entrapment efficiency was not experimentally determined, the sustained release profile and limited initial burst release suggest effective association of capecitabine within the lipidic nanoemulsion gel matrix. The optimized formulation F5 exhibited $99.64 \pm 0.119\%$ cumulative drug release over 8 h, indicating prolonged release behavior suitable for intranasal administration. The drug release profiles were presented in Figure 3.

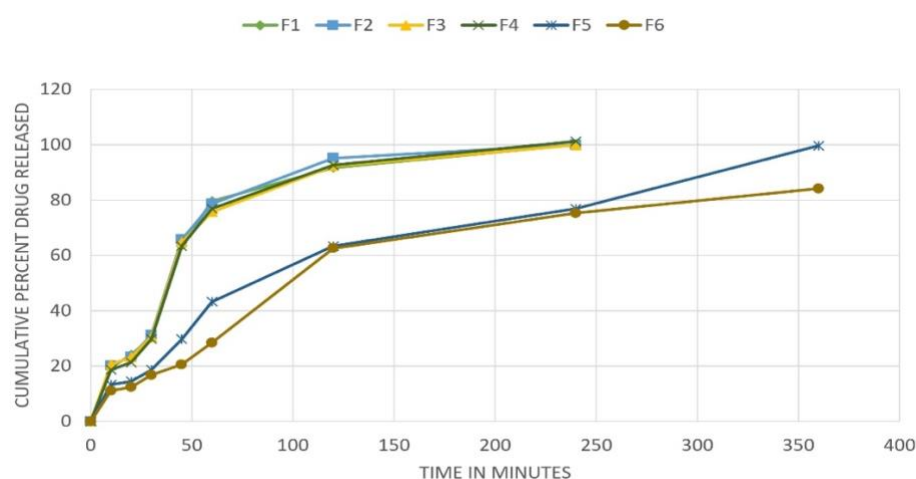


Figure 3 In-vitro cumulative release profiles of capecitabine from formulations F1–F6. The formulations demonstrated sustained drug release over 8 h, with F5 selected for further kinetic analysis.

Drug Release Kinetics

The in vitro release data of the optimized formulation were fitted into various kinetic models to elucidate the mechanism of drug release. The release profile showed higher linearity with the Higuchi and Korsmeyer–Peppas models, suggesting that drug release from the nanoemulsion in situ gel system was predominantly governed by diffusion-controlled release from the lipid-polymeric matrix [28]. Figure 4 shows drug release mechanisms.

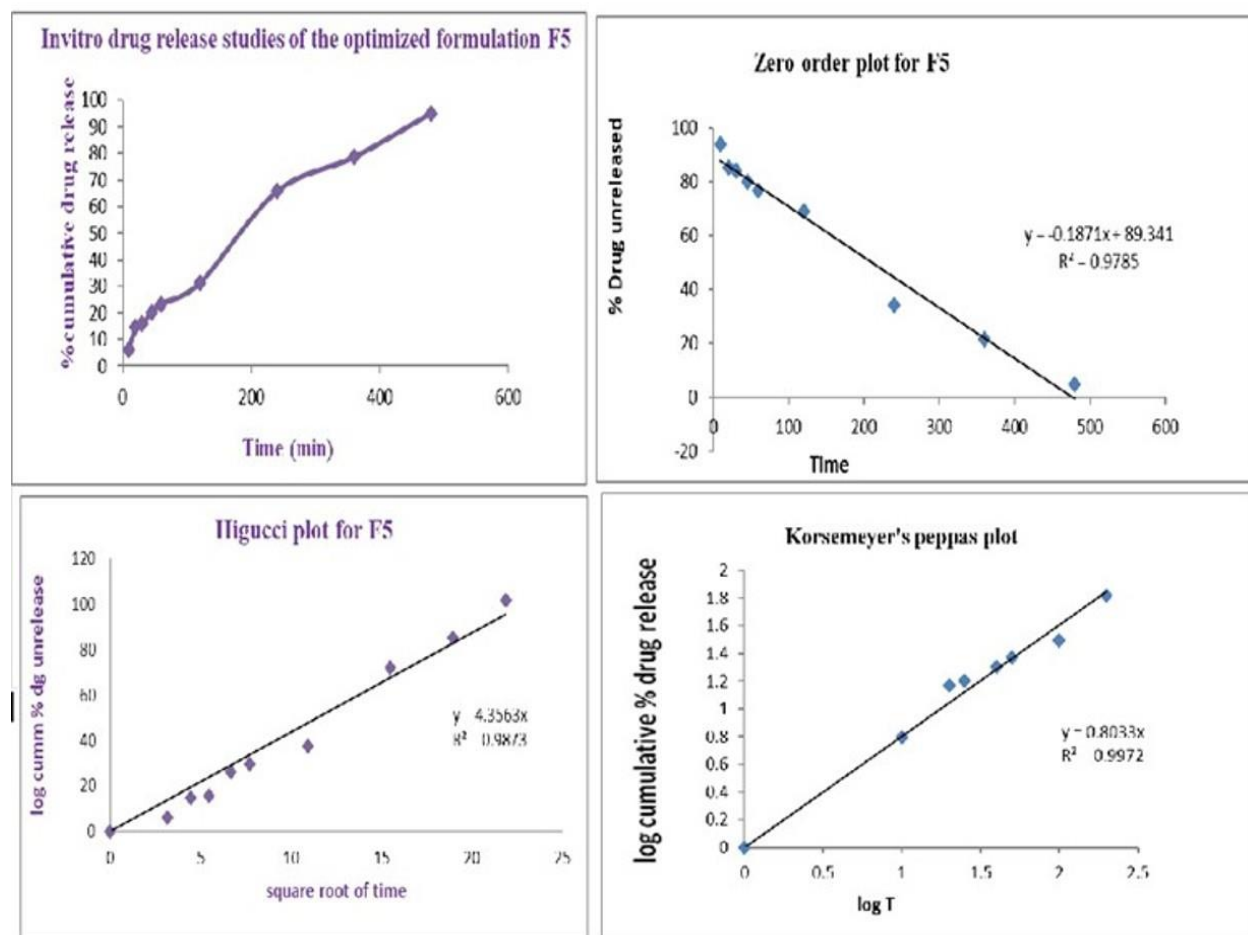


Figure 4: Drug-release kinetic analysis of optimized formulation F5. (A) cumulative drug release, (B) zero-order kinetics, (C) Higuchi kinetics, and (D) Korsmeyer–Peppas kinetics.

3.10 Rheological Evaluation [29]

The rheological behavior of the optimized formulation was studied to assess its flow characteristics during administration and during gel formation. The rheological profile demonstrated a linear increase in shear stress with increasing shear rate, indicating Newtonian flow behavior at room temperature. This behavior facilitates administration via the intranasal route prior to gel formation. The rheogram is given in Figure 5. The slope of the rheogram corresponds to the viscosity of the system according to Newton's law of flow.

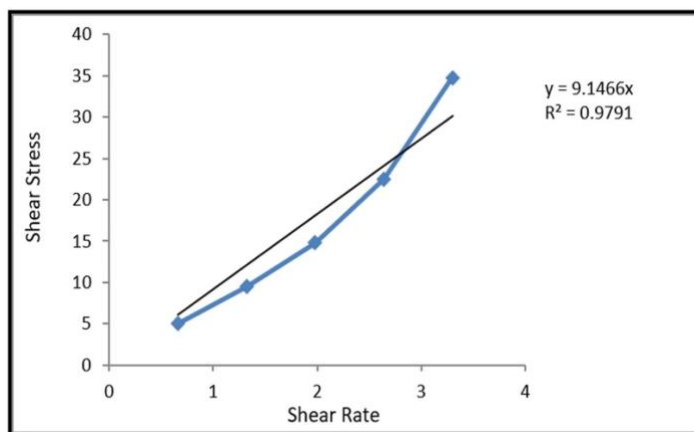


Figure 5 Shear stress–shear rate relationship of the optimized capecitabine-loaded nanoemulsion in situ gel (F5). The regression showed $R^2 = 0.9791$, with a calculated viscosity of approximately 9.15 cP.

Scanning Electron Microscopy

Scanning electron microscopy was performed to evaluate the surface morphology and structural characteristics of the optimized nanoemulsion in situ gel formulation. SEM images revealed spherical lipid droplets uniformly dispersed within the gel matrix, indicating successful formation of the nanoemulsion-based in situ gel system [30]. The SEM image is presented in Figure 6.

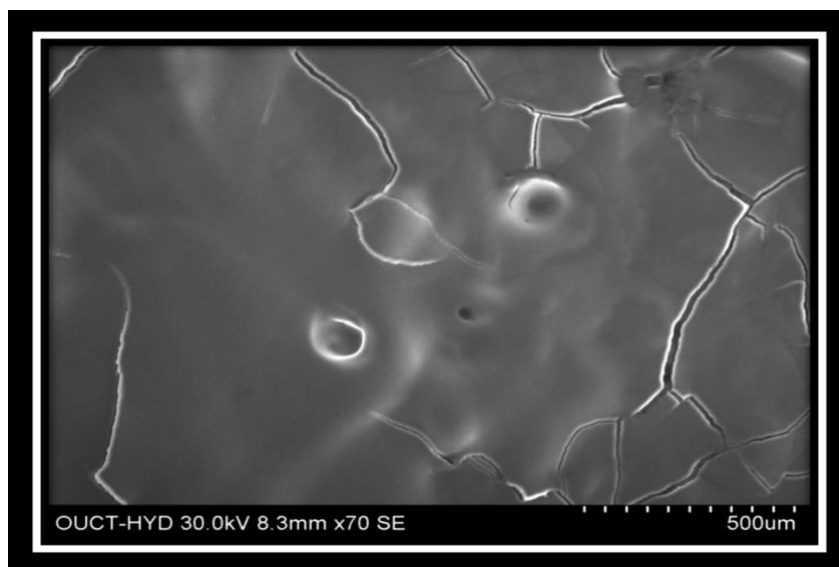


Figure 6: SEM image of the optimized capecitabine-loaded nanoemulsion in situ gel (F5). The images show the surface morphology of the optimized formulation. Scale bar = 500 μm .

CONCLUSION

The present investigation successfully developed and evaluated a thermoresponsive capecitabine-loaded nanoemulsion in situ gel intended for potential intranasal delivery in glioblastoma therapy. The optimized formulation exhibited suitable physicochemical characteristics, including

appropriate gelation temperature, acceptable nasal pH, nanosized droplet distribution, satisfactory drug content, and sustained drug release behavior. DSC and SEM studies confirmed successful incorporation of capecitabine into the lipid-polymeric matrix without significant drug–excipient incompatibility.

The nanoemulsion-based in situ gel system may offer several advantages, including prolonged nasal residence time, controlled drug release, and potential enhancement of nose-to-brain delivery through the intranasal route while minimizing systemic exposure and first-pass metabolism. The sustained release profile and nanoscale droplet size suggest that the developed formulation could serve as a promising platform for nose-to-brain delivery of capecitabine.

Nevertheless, the present study is limited to physicochemical and in vitro characterization. Further investigations involving ex vivo permeation, nasal safety evaluation, pharmacokinetic studies, biodistribution analysis, and in vivo therapeutic efficacy studies are required to establish the clinical applicability of the developed formulation for glioblastoma treatment.

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