

Optimization and Evaluation of Microsponge-Embedded Thermoresponsive *In-Situ* Gel for Intranasal Delivery of Sumatriptan Succinate

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ABSTRACT

Migraine is a prevalent neurological disorder requiring rapid and effective therapeutic intervention. However, the conventional oral administration of Sumatriptan succinate (SS) is limited by extensive first-pass metabolism, low bioavailability, and a short biological half-life. This study aimed to develop and optimize an SS-loaded microsponge-embedded thermoresponsive *In-Situ* nasal gel to prolong nasal residence time and provide sustained drug release for improved migraine management. SS-loaded microsponges were prepared by the quasi-emulsion solvent diffusion method using ethyl cellulose as the polymer and polyvinyl alcohol as the stabilizer. A 2² factorial design was employed to optimize the formulation by evaluating the effects of polymer concentration and stirring speed on particle size, drug entrapment efficiency (DEE), and drug content. The optimized microsponges were incorporated into Poloxamer 407-based *In-Situ* gels (15%, 20%, and 25% w/v) prepared by the cold method and evaluated for physicochemical characteristics, pH, viscosity, gelation temperature, gelation time, and *in vitro* drug release. The microsponges exhibited particle sizes of 50.45–83.52 μ m, DEE of 48.20–77.32%, and drug content of 59.20–68.63%. SEM analysis confirmed spherical, porous microsponges with sustained drug release (64.19–74.33%). The *In-Situ* gels demonstrated an acceptable pH (4.98–5.26), gelation temperature (28.7–33.2°C), rapid gelation time (29–36 s), and viscosity ranging from 3509 to 3699 cPs. The optimized formulation (ISG 3) exhibited sustained drug release (39.45% in 8 h) following zero-order kinetics ($R^2 = 0.9883$) and remained stable over 3 months. These findings suggest that the microsponge-embedded thermoresponsive *In-Situ* nasal gel is a promising platform for sustained intranasal delivery of SS, with the potential to improve therapeutic efficacy and patient compliance in migraine management.

Keywords: Sumatriptan Succinate, Microsponges, Thermoresponsive *In-Situ* nasal gel, Migraine, Intranasal drug delivery

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INTRODUCTION

Novel Drug Delivery Systems (NDDS) are designed to deliver a therapeutically effective concentration of a drug to a specific site of action in a controlled, predictable, and sustained manner, thereby enhancing therapeutic efficacy while minimizing systemic side effects. These advanced systems aim to overcome the inherent limitations of conventional dosage forms, such as low bioavailability, frequent dosing requirements, poor patient compliance, and undesirable systemic exposure.¹

Effective drug delivery to the central nervous system (CNS) remains a major pharmaceutical challenge due to the presence of the blood–brain barrier (BBB). This highly selective barrier, formed by specialized endothelial cells lining cerebral capillaries, plays a crucial role in

maintaining CNS homeostasis by restricting the entry of most xenobiotics. Consequently, hydrophilic and high molecular weight drugs exhibit poor permeability across the BBB, rendering conventional oral delivery largely ineffective for CNS targeting.^{2,3}

In this context, the intranasal route has emerged as a promising alternative for direct nose-to-brain drug delivery owing to the unique anatomical and physiological connections between the nasal cavity and the brain. Intranasal administration bypasses both the BBB and hepatic first-pass metabolism, enabling rapid onset of action and improved bioavailability.^{2,4,5} Nasal drug delivery systems have gained significant attention for migraine management due to their rapid therapeutic

onset, enhanced bioavailability, reduced systemic exposure, and non-invasive, patient-friendly administration. *In-Situ* nasal gels represent a notable advancement in this field, offering distinct advantages over conventional liquid nasal formulations by increasing residence time and reducing mucociliary clearance.⁶⁻⁸

Intranasal administration provides several therapeutic benefits in migraine treatment, including rapid drug absorption, direct delivery of unmetabolized drug to the CNS, avoidance of hepatic first-pass metabolism, suitability during episodes of nausea and vomiting, and an improved adverse-effect profile. Additionally, the thin epithelial barrier, reduced enzymatic activity, near-neutral pH, and limited dilution within the nasal cavity further contribute to enhanced drug stability and absorption. However, challenges such as limited dosing volume, potential nasal irritation, and inter-individual variability in absorption must be addressed during formulation development.⁹

The term *In-Situ* refers to formulations that undergo a reversible sol-to-gel transition upon administration at the site of application. *In-Situ* nasal gels are administered as low-viscosity solutions and transform into gels in response to physiological stimuli such as temperature, pH, or ionic strength. This transformation enhances nasal retention, improves drug absorption, and enables sustained and controlled drug release. Polymers such as thermosensitive poloxamers, pH-responsive carbopol, and ion-activated gellan gum are commonly employed in these systems.^{9,10}

Microsponges are porous, polymeric microspheres capable of encapsulating a wide range of active pharmaceutical ingredients and releasing them in a controlled and sustained manner. Their unique three-dimensional structure, characterized by interconnected voids, allows high drug loading while minimizing dose-related irritation. Microsponges enhance drug stability, reduce dosing frequency, and improve patient compliance.^{11,12} Typically ranging from 5 to 300 μm in size, microsponges possess extensive internal pore networks capable of entrapping drug quantities up to three times their own weight. Their high degree of cross-linking renders them chemically inert, mechanically robust, free-flowing, and resistant to processing stresses. Due to their particulate size, microsponges are not systemically absorbed, providing an additional safety advantage.¹³⁻¹⁶

Migraine is a chronic, recurrent neurological disorder characterized by unilateral, pulsating headache accompanied by nausea, vomiting, photophobia, and phonophobia. Migraine attacks typically last between 4 and 72 hours and may occur with or without aura. Affecting approximately 10% of the global population, migraine is recognized by the World Health Organization as one of the most disabling neurological disorders

worldwide.^{17,18} Migraine is broadly classified into migraine without aura, migraine with aura, and chronic migraine.¹⁹⁻²⁰

Sumatriptan succinate, a selective 5-HT_{1B/1D} receptor agonist, is widely used as an abortive therapy for acute migraine attacks. Despite its proven efficacy, oral sumatriptan exhibits low bioavailability (~14%) due to extensive first-pass hepatic metabolism and has a short elimination half-life of approximately 2 hours.²¹ Although subcutaneous administration provides higher efficacy, its invasive nature limits patient acceptability. Intranasal delivery of sumatriptan offers rapid onset of action, improved patient compliance, and circumvention of hepatic metabolism; however, conventional nasal formulations suffer from rapid clearance and short duration of action,²² consequently, the development of microsponge-loaded *In-Situ* nasal gels represents a promising strategy to enhance bioavailability, prolong drug release, and improve therapeutic outcomes in migraine management.

MATERIALS AND METHODS

This Sumatriptan succinate was obtained from Porus Laboratories Hyderabad (India). Ethyl cellulose, Polyvinyl Alcohol, Dichloromethane, Methanol, Triethyl citrate and Poloxamer-407 were procured from Burgoyne Burbidges and co. Mumbai, India.

Characterization of pure drug

Determination of Melting Point

The melting point of SS was determined using the Digital melting point apparatus to confirm drug purity.²³

Determination of λ_{max}

SS was analyzed in phosphate buffer (pH 6.8) using UV–Visible spectrophotometry. A standard stock solution (1000 $\mu\text{g/mL}$) was prepared and suitably diluted. Scanning between 200–400 nm showed maximum absorbance at 227 nm.²⁴

Differential Scanning Calorimetry (DSC)

DSC was performed to assess the thermal behavior and thermotropic properties of the drug. Approximately 3–5 mg of the sample was hermetically sealed in an aluminum pan and heated at a rate of 10 $^{\circ}\text{C}/\text{min}$ over a temperature range of 40–200 $^{\circ}\text{C}$ under a nitrogen atmosphere with a flow rate of 10 mL/min. The resulting thermogram was recorded.^{24,25}

Fourier transform-infrared spectroscopy (FTIR)

Infrared spectra were obtained to evaluate the purity of the drug and excipients using a Fourier transform infrared (FT-IR) spectrophotometer (Shimadzu 8400S, Japan). The spectra were recorded in the range of 4000–400 cm^{-1} at a resolution of 4 cm^{-1} . Samples were uniformly mixed

with potassium bromide (KBr) and compressed into pellets by applying a pressure of five tons for 5 minutes using a hydraulic press. The prepared pellets were placed in the IR beam path, and the spectra were recorded.^{24,25}

Drug-excipient interaction study

Drug-excipient compatibility was evaluated using FT-IR and DSC studies. FT-IR analysis was carried out to assess possible interactions between the drug and excipients, while DSC analysis provided information on the physical nature of the samples (crystalline or amorphous) and helped identify any potential interactions between the drug and excipients.^{24,25}

Ultraviolet-visible spectroscopy

Calibration curve of FLZ was plotted using phosphate buffer solution (PBS) of pH 6.8 by keeping concentration range of 1–10 µg/ml. The drug was analyzed spectrophotometrically (Pharmaspec 1700, Shimadzu, Japan) at 227 nm and linearity was confirmed by regression analysis.^{24,25}

Preparation of SS Microsponges

SS-loaded microsponges were prepared using the quasi-emulsion solvent diffusion technique. The internal phase consisted of SS and ethyl cellulose dissolved in a methanol:dichloromethane mixture (1:1), with triethyl citrate (1%) added as a plasticizer. The drug was completely dissolved using ultrasonication at 35 °C. This organic phase was slowly introduced into an aqueous polyvinyl alcohol solution (0.5% w/v) serving as the external phase and stirred at either 800 or 1200 rpm for 2 h. Microsponges were formed as a result of solvent diffusion and evaporation of dichloromethane and methanol. The formed microsponges were collected by filtration, washed with distilled water, and dried in a hot air oven at 40 °C for 12 h. The dried microsponges were weighed to determine the production yield, and different formulation batches were prepared as shown in Table 1.^{26,27}

Experimental Design and Statistical Optimization

A 2² full factorial design was employed to investigate the influence of formulation and process variables on the characteristics of the microsponge formulation. The experimental design and statistical analysis were performed using Design-Expert® software (Version 13.0.5.0, Stat-Ease Inc., USA).

Two independent variables were selected based on preliminary experiments:

- A: Polymer concentration (mg)

- B: Stirring speed (rpm)

Each factor was studied at two levels, coded as –1 (low level) and +1 (high level). Polymer concentration was varied between 100–200 mg, while stirring speed ranged from 800–1200 rpm. A total of four experimental runs were generated according to the randomized factorial design.

The influence of these variables was evaluated on three critical responses:

- R1: Particle size (µm)
- R2: Drug entrapment efficiency (DEE, %)
- R3: Drug content (%)

The experimental data were fitted to a two-factor interaction (2FI) model, and the significance of model terms was evaluated using analysis of variance (ANOVA). Model adequacy was assessed using statistical parameters including coefficient of determination (R²), adjusted R², predicted R², coefficient of variation (CV), and adequate precision. A p-value < 0.05 was considered statistically significant.

Optimization of the formulation variables was carried out using the numerical desirability function approach. The goal was to minimize particle size while maximizing drug entrapment efficiency and drug content, with both independent variables constrained within their experimental ranges. The optimized formulation predicted by the software was further subjected to confirmation analysis to validate the model predictions.^{28,29}

Evaluation of SS microsponges^{30–33}

Production yield

Production yield of microsponges was determined by formula mentioned below.

$$\text{Production Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

Actual drug content and entrapment efficiency

Precisely weighed quantity (100 mg) of microsponges containing drug was kept in 100 ml PBS (pH 6.8) for 12 h with continuous stirring. Samples were filtered using 0.4 µm membrane filter and further analyzed at 287 nm next to blank using ultraviolet-visible (UV) spectrophotometer (UV-1800, Shimadzu Corporation, Kyoto, Japan). Estimation of drug content and encapsulation efficiency for all batches were done using following expressions

$$\text{Actual drug content (\%)} = \frac{\text{Amount of drug in microsponges}}{\text{Amount of microsponges}} \times 100$$

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount of drug in microsponges}}{\text{Amount of microsponges}} \times 100$$

Nine Particle size and size distribution:

A definite dried amount of the Dorzolamide hydrochloride microsponges were suspended in water and were sonicated for one minute to prevent aggregation of the microsponges, then, the mean particle size and size distribution were performed for the microsponges formulation using laser scattering particle size distribution analyser (HORIBA LA-300)

Scanning electron microscopy (SEM)

The morphological study was performed by SEM instrument JSM-IT500 JEOL. Microsponges were scanned and analysed using a JSM-IT1500 Electron Microscope linked to a Fine Coat, also known as the JEOL JFC-1100E Ion Sputter. The sample was placed on a copper sample holder, and the gold sputter was covered with carbon.

In vitro drug release studies

In vitro drug release studies were performed to evaluate the rate and extent of SS release from the microsponges. The study was conducted using USP dissolution apparatus type II (paddle method). A quantity of microsponges equivalent to 25 mg of SS was dispersed in 900 mL of phosphate buffer (pH 6.8), selected to simulate nasal physiological conditions. The dissolution medium was maintained at 32.0 ± 0.5 °C, corresponding to nasal temperature, and the paddle rotation speed was set at 150 rpm. Samples (5 mL) were withdrawn at predetermined intervals initially at 30 minutes and subsequently at hourly intervals up to 8 hours and replaced with fresh medium to maintain sink conditions. The withdrawn samples were analyzed spectrophotometrically at 287 nm, and the cumulative percentage drug release (CDR%) was calculated for each time point.

Formulation of *In-Situ* gel loaded with optimized microsponges

A thermosensitive *In-Situ* gel containing optimized microsponges of Sumatriptan Succinate was prepared using Poloxamer 407 (PF-127) as the gelling polymer through the cold method.

Initially, plain polymeric gels were prepared at different concentrations (15%, 20%, and 25% w/v) to evaluate their gelation characteristics. The required quantity of Poloxamer 407 was gradually dispersed in double-distilled water under gentle stirring to avoid lump

formation. The dispersion was then stored at 4 °C overnight to ensure complete hydration and swelling of the polymer, resulting in the formation of a clear and viscous solution.

After determining the concentration exhibiting optimal gelation behavior, the optimized microsponge formulation equivalent to 1% w/w of drug content was incorporated into the cold polymeric solution. The microsponges were carefully dispersed in the chilled gel base with continuous gentle stirring using a glass rod to obtain uniform distribution.

To ensure homogeneity and remove entrapped air bubbles, the resulting dispersion was subjected to sonication for approximately 1 minute at 4 °C. The prepared formulation was stored under refrigerated conditions until further evaluation.

Evaluation of Microsponge-Loaded *In-Situ* Gel

Three concentrations of Poloxamer 407 gels (15%, 20%, and 25% w/v) were prepared and evaluated for their ability to undergo sol–gel transition at physiological temperature.

The optimized microsponge formulation was successfully incorporated into the selected gel base without any visible aggregation or phase separation. The cold method facilitated uniform dispersion of microsponges within the polymeric matrix while preserving their structural integrity. The incorporation of microsponges within the thermosensitive polymeric network is expected to enhance nasal residence time and provide sustained drug release, thereby improving the therapeutic performance of the formulation.

Visual inspection

The organoleptic properties, such as color, texture, consistency, homogeneity, and physical appearance of gel containing microsponges were checked by visual observation.

pH measurement

Gel formulation pH was recorded using digital pH meter. 5 g gel was dispersed in 45 ml distilled water at 27°C and solution pH was measured.

Determination of the rheological behavior

The rheological behavior of the formulated gels was assessed using a Brookfield rotational viscometer (Model

RVDV-III U). Viscosity measurements were carried out at varying shear rates by increasing the rotational speed from 10 to 50 rpm, followed by a reverse cycle from 50 to 10 rpm, maintaining a dwell time of 10 s at each speed. Prior to analysis, the samples were allowed to equilibrate at 35 ± 1 °C. Measurements were performed using T-F spindle No. 96, and viscosity values were recorded. All determinations were conducted in triplicate to ensure reproducibility.

Determination of the gelation time:

5 mL of the prepared gel was transferred into a 10 mL glass vial containing a magnetic stir bar and securely sealed. The vial was placed in a thermostatically controlled water bath, and the temperature was gradually raised from 20 °C to 40 °C, with accurate monitoring using a thermometer having a sensitivity of 0.1 °C. The formulation was stirred at a constant speed of 80 rpm, and the temperature at which the magnetic stir bar stopped moving was recorded as the gelation temperature.

Gelation temperature:

The gelation temperature was determined using the magnetic stirring method. An aliquot of 5 mL of the formulation was transferred into a 10 mL glass vial containing a magnetic bead and securely sealed. The vial was placed in a thermostatically controlled water bath, and the temperature was gradually increased from 20 °C to 40 °C while monitoring with a thermometer having a sensitivity of 0.1 °C. The formulation was stirred at 80 rpm, and the temperature at which the magnetic bead stopped rotating was recorded as the gelation temperature.

In vitro release of drug from gel

The optimized *In-Situ* gel formulation (0.5%) containing SS-loaded microsponges from batches F1–F3 was evaluated for *in vitro* drug release using Franz diffusion cells. A cellophane membrane with a pore size of 0.45 µm, pre-soaked overnight in glycerin, was mounted between the donor and receptor compartments. The receptor compartment, with a volume of 25 mL, was filled with phosphate-buffered saline (PBS, pH 6.8), while the donor compartment contained the microsponge-loaded gel formulation. The diffusion assembly was maintained at 37 ± 1 °C and continuously stirred at 50 rpm using a magnetic stir bar. At predetermined time intervals, 1 mL samples were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh PBS to maintain sink conditions.

The collected samples were suitably diluted and analyzed to determine the drug release profile.³⁵

Release Kinetics

The *in vitro* drug release data of the optimized formulation were fitted to various mathematical models to determine the drug release kinetics and mechanism. The cumulative percentage drug release data were analyzed according to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas kinetic models. The regression coefficient (R^2) was calculated for each model, and the model exhibiting the highest R^2 value was considered to best describe the release kinetics of the formulation.

Short-term stability studies:

The short-term stability of the optimized *In-Situ* gel formulation was assessed in accordance with ICH guidelines. Samples were stored in tightly closed glass vials at 25 ± 2 °C with $60 \pm 5\%$ relative humidity and at 4 ± 2 °C with $55 \pm 5\%$ relative humidity for a period of three months. At monthly intervals, the formulations were withdrawn and evaluated for physical appearance, pH, drug content, gelation temperature, mucoadhesive strength, and *in vitro* drug release to monitor any changes during storage.³⁶

RESULTS AND DISCUSSION

Characterization of pure drug

Determination of melting point

The melting point of sumatriptan succinate was determined in triplicate to confirm the identity and purity of the drug sample. The observed melting point was 175.3 ± 1.5 °C, which is in close agreement with the reported literature value of 168–171 °C. The small deviation may be attributed to experimental conditions but remains within the acceptable range, thereby confirming the purity and authenticity of the drug sample used in the study.²³

Determination of λ_{max}

The UV absorption spectrum of sumatriptan succinate was recorded in phosphate buffer (pH 6.8) within the wavelength range of 200–400 nm to determine the maximum absorption wavelength. The spectrum exhibited a distinct absorption peak at 227 nm, which corresponds to the maximum absorbance (λ_{max}) of the drug under the selected conditions. This wavelength was subsequently used for further quantitative analysis.²⁴ The UV absorption spectrum of the drug is presented in Figure 1.

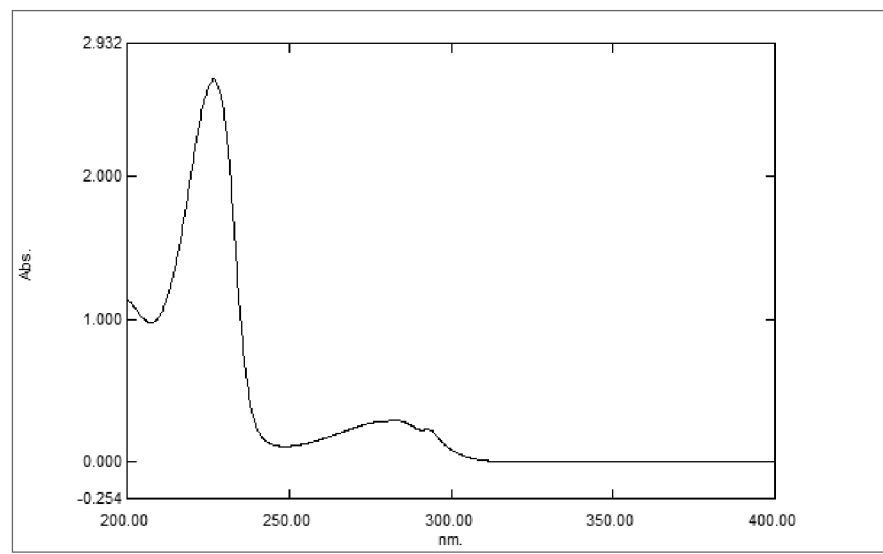


Figure 1: Absorption maxima of SS

Differential Scanning Calorimetry (DSC)

Thermal analysis of the pure drug was carried out using DSC to evaluate its thermal behavior and crystallinity. The DSC thermogram of pure sumatriptan succinate

showed a sharp endothermic peak at approximately 176 °C, corresponding to the melting point of the drug. The presence of a well-defined melting endotherm indicates the purity of the drug substance.²⁴ The DSC thermogram is illustrated in Figure 2.

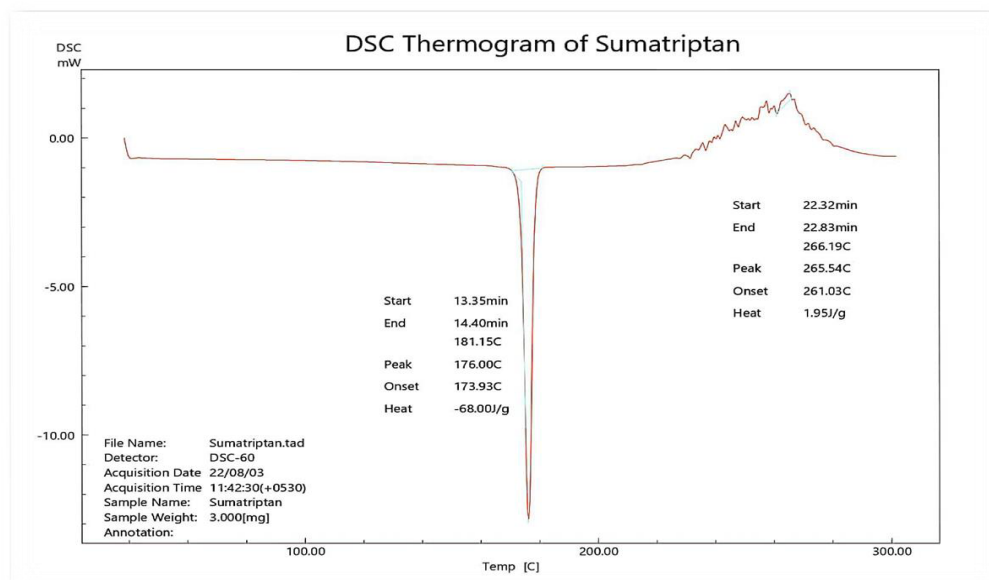


Figure 2: DSC of Sumatriptan succinate

Drug–Excipient compatibility study:

Compatibility between sumatriptan succinate and the selected excipients was evaluated using DSC and FTIR analysis.

The DSC thermogram of the pure drug displayed a characteristic endothermic peak at 176.03 °C, consistent

with its reported melting point. A similar peak was also observed in the thermogram of the optimized microsponge formulation, indicating that the thermal behavior of the drug remained unchanged in the presence of excipients. The absence of any significant shift or

disappearance of the melting peak confirms no significant drug–excipient interaction.

Further confirmation of compatibility was obtained through Fourier Transform Infrared (FTIR) spectroscopy. The FTIR spectra of the pure drug, individual excipients, and the optimized formulation were compared. Characteristic absorption peaks corresponding to the functional groups of sumatriptan succinate were retained in the formulation spectrum without significant changes.

The major peaks observed include N–H stretching of the indole group ($\sim 3355\text{ cm}^{-1}$), O=S=O stretching ($\sim 2775\text{--}2915\text{ cm}^{-1}$), conjugated C=C stretching ($\sim 1680\text{--}1700\text{ cm}^{-1}$), and O–H bending vibrations ($\sim 1458\text{--}1484\text{ cm}^{-1}$). The preservation of these characteristic peaks indicates chemical stability and compatibility of the drug with formulation excipients.^{24,25} The DSC thermogram of the optimized blend is shown in Figure 3.

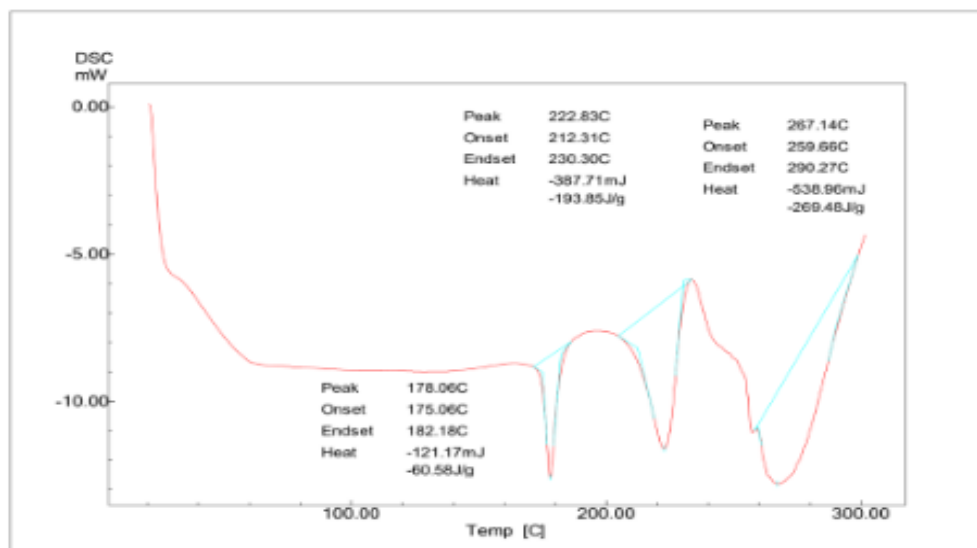


Figure 3: DSC of optimized blend

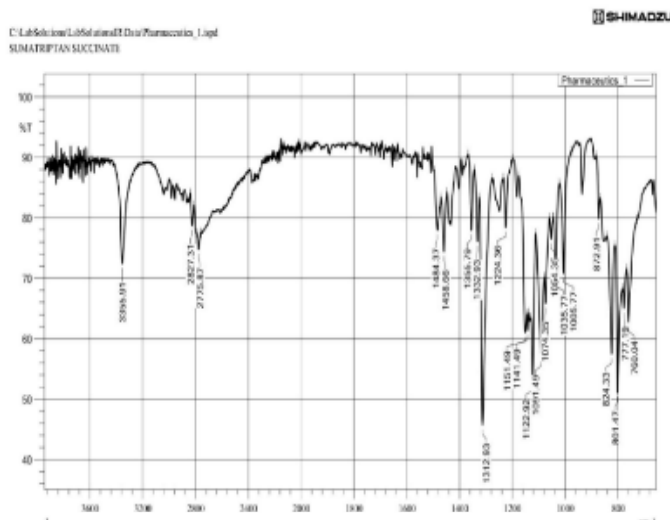


Figure 4: FTIR spectra of the blend

Ultraviolet–Visible Spectroscopy

A calibration curve of sumatriptan succinate was constructed in phosphate buffer (pH 6.8) over a concentration range of 1–7 µg/mL according to Beer–Lambert’s law. The absorbance values obtained at 227

nm showed a linear relationship with concentration within the studied range. The calibration plot is shown in Figure 5. The developed method was used for the quantitative estimation of drug content and *in vitro* release studies.

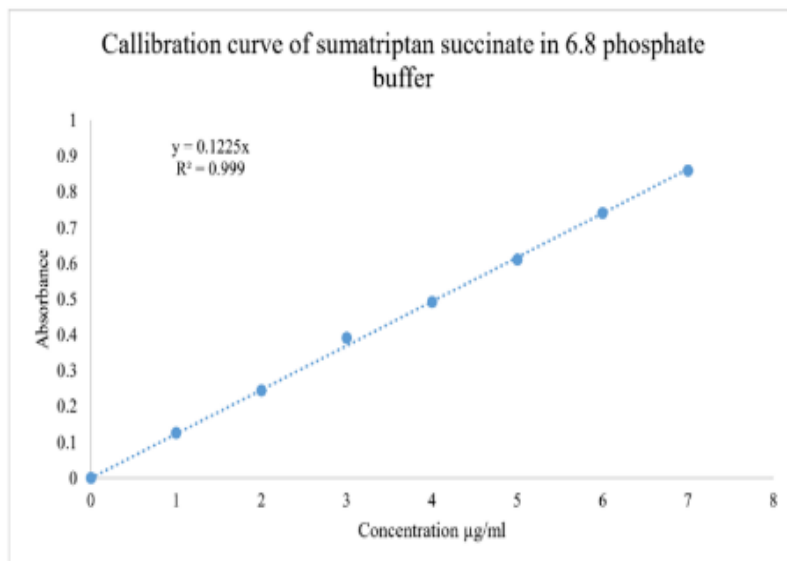


Figure 4: Standard calibration curve

Formulation design

Microsponge formulations of sumatriptan succinate were prepared using the quasi-emulsion solvent diffusion method. The formulations were designed using different drug-to-polymer ratios and stirring speeds to investigate their influence on microsponge characteristics. Ethyl

cellulose was used as the polymeric matrix, while polyvinyl alcohol (PVA) served as the stabilizing agent. Methanol and dichloromethane (DCM) were employed as organic solvents, and triethyl citrate was used as a plasticizer. The composition of various formulations is summarized in Table 1.

Table 1: Formulation design

Ingredients	F1	F2	F3	F4
Sumatriptan Succinate(mg)	100	100	100	100
Ethyl cellulose(mg)	100	200	100	200
Methanol:DCM:(ml)	10:10	10:10	10:10	10:10
Triethyl citrate(mg)	1	1	1	1
Polyvinyl Alcohol(mg)	500	500	500	500
Distilled water(ml)	100	100	100	100
Drug: Polymer	1:1	1:2	1:1	1:2
Stirring speed	1200	1200	800	800

Evaluation of SS microsponges

Physical appearance

The prepared microsponges appeared as white to off-white free-flowing particles. The microsponge particles were discrete and uniform, indicating successful preparation using the quasi-emulsion solvent diffusion technique.³³

Production yield

The percentage production yield of the prepared microsponge formulations ranged from $61.66 \pm 0.52\%$ to $76.33 \pm 1.52\%$. The results indicated that polymer concentration significantly influenced the production yield. Formulations containing higher polymer content exhibited improved yield, possibly due to enhanced formation of polymeric matrices during the solvent diffusion process.³⁴

Drug content and entrapment efficiency

The drug content of the prepared formulations ranged from $59.20 \pm 0.61\%$ to $68.63 \pm 0.22\%$, while the drug entrapment efficiency (DEE) varied between 48.20% and 77.32%. An increase in the drug-to-polymer ratio and stirring speed resulted in a corresponding increase in entrapment efficiency. This may be attributed to the

higher viscosity of the polymeric phase, which reduces the diffusion of drug molecules into the external phase during microsponge formation. Consequently, improved drug precipitation and entrapment within the polymeric matrix occur.³³⁻³⁵

Particle size and size distribution

Particle size analysis was carried out using optical microscopy. The average particle size of the prepared microsponges ranged from $50.45 \pm 0.97 \mu\text{m}$ to $83.52 \pm 0.35 \mu\text{m}$, which falls within the typical microsponge size range (5–300 μm). The results indicated that particle size decreased with increasing stirring speed.³²

Scanning Electron Microscopy (SEM)

The surface morphology of the microsponges was examined using SEM. The SEM images of the optimized formulation revealed spherical particles with a highly porous surface structure. The porous nature of the microsponges can be attributed to the diffusion and evaporation of solvent during the preparation process, which results in the formation of internal cavities within the particles.^{33,36} The SEM micrographs confirm the successful formation of a characteristic porous microsponge structure, suitable for drug loading and controlled release applications.³²

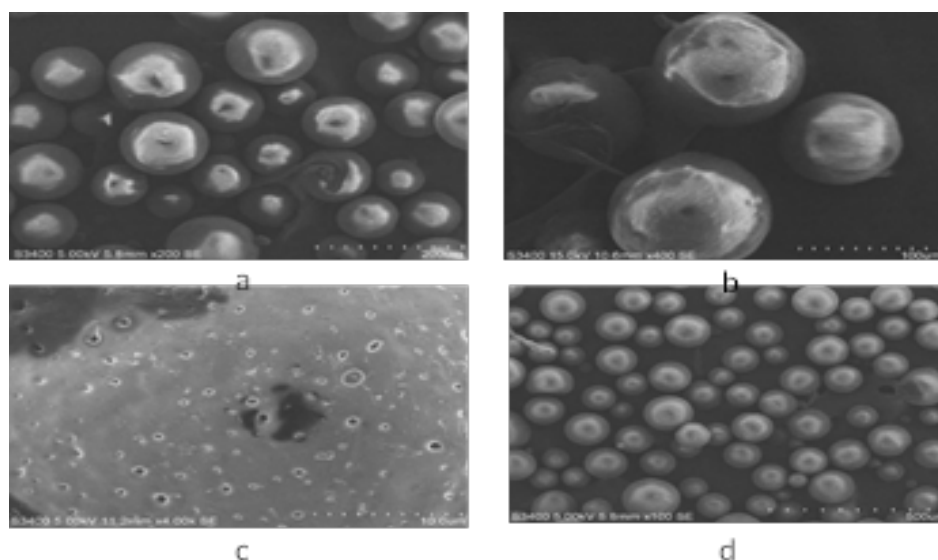


Figure 6: SEM image of microsponge F4 a) At resolution of X200 b) At resolution of X400 c) At X4.00K d) At resolution of X 10

In Vitro drug release study

The *in vitro* drug release behavior of the microsponge formulations was evaluated to determine their suitability for sustained drug delivery. The cumulative drug release from different formulations ranged from 64.19% to 74.33%. Formulations containing higher concentrations of ethyl cellulose exhibited slower drug release, which

can be attributed to the formation of thicker polymeric barriers that limit drug diffusion. In contrast, formulations with lower polymer content produced comparatively thinner microsponge walls, resulting in faster drug release.

The release of sumatriptan succinate from the microsponges was primarily governed by a combination

of diffusion and polymer matrix erosion mechanisms. The corresponding release profiles are illustrated in Figure 6. The dissolution data is presented in Table 2, and the

Table 2: Evaluation of formulated microsponges

s	Drug: polymer ratio	Stirring speed	Particle size (µm)	Drug content (%)	Drug entrapment efficiency (%)	Production yield (%)	CDR at 8 hrs
F1	1:1	1200	57.23±0.97	59.2±0.61	69.4±0.78	61.33±1.52	74.35
F2	1:2	1200	50.45±0.27	68.63±0.59	77.32±0.93	76.33±1.55	75.50
F3	1:1	800	83.52±0.51	56.4± 0.68	48.2±0.53	62.66±0.57	64.19
F4	1:2	800	75.35±0.23	67.5± 0.35	52.3±0.67	74.33±1.83	69.96

*Standard deviation mean “n”=3. CDR: Cumulative drug release, SD: Standard deviation

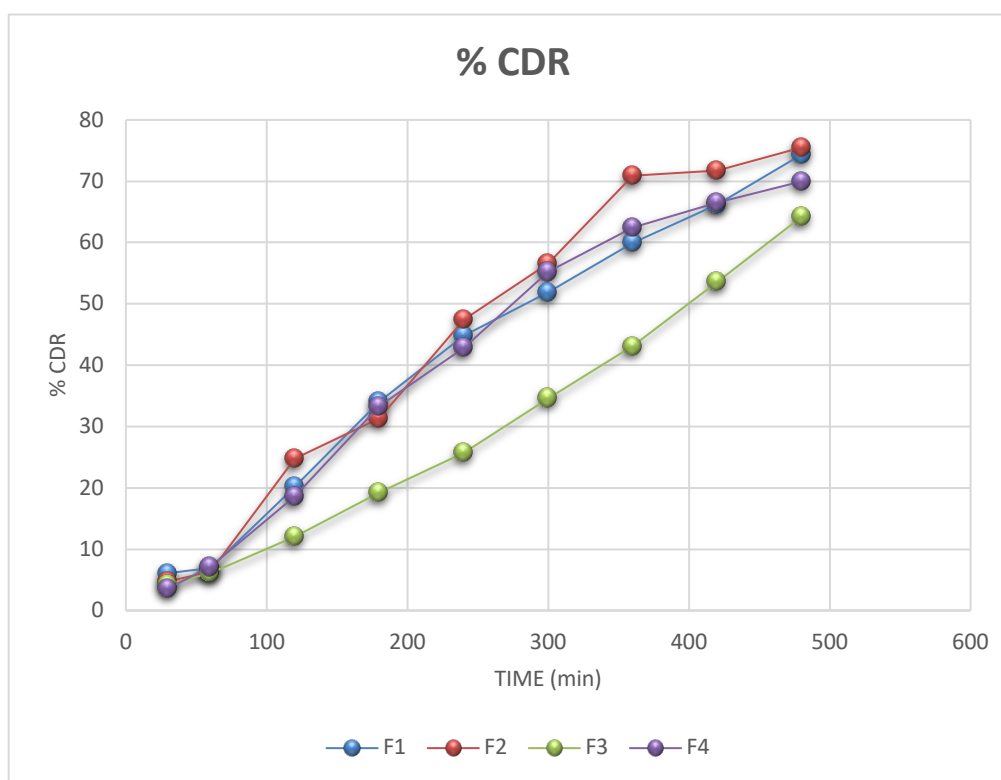


Figure 5: In-Vitro drug release of formulated microsponges

Statistical analysis and optimization

A 2² full factorial design was applied to evaluate the influence of polymer concentration (A) and stirring speed (B) on the critical quality attributes of the microsponge formulations, namely particle size, drug entrapment efficiency (DEE), and drug content. The experimental data were analyzed using Design-Expert® software (Version 13), and the significance of the developed models was assessed by analysis of variance (ANOVA).

The statistical analysis demonstrated that the developed models were significant for all the studied responses ($p < 0.05$), indicating that the selected formulation variables had a measurable impact on the microsponge characteristics. Among the investigated factors, stirring speed (B) showed a significant effect on particle size and drug entrapment efficiency, whereas polymer concentration (A) significantly influenced drug content. The developed models exhibited strong predictive capability, with coefficient of determination (R^2) values

exceeding 0.92 for all responses, suggesting good agreement between experimental and predicted values.

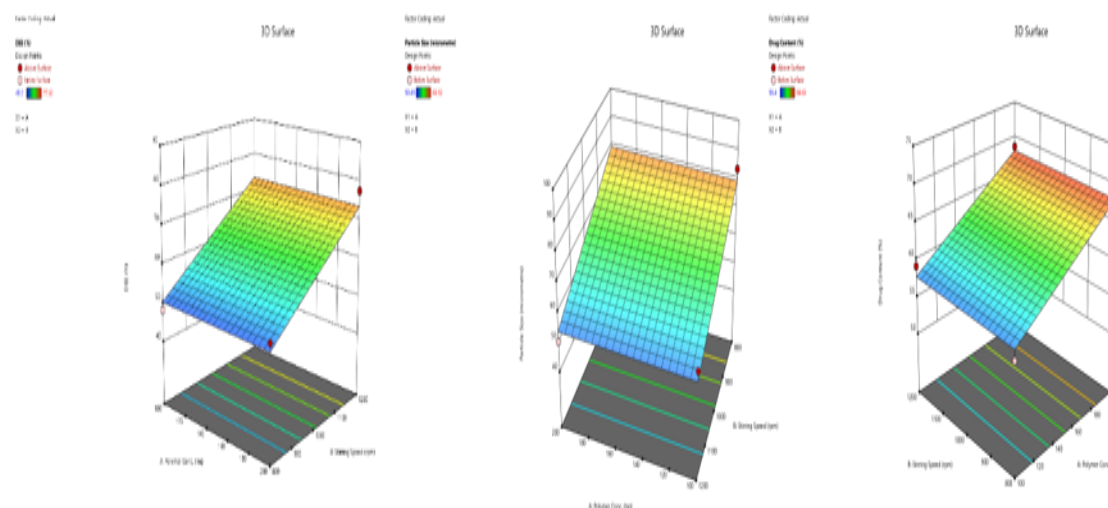


Figure 8: Statistical Analysis

Furthermore, the adequate precision values for all responses were greater than 4, confirming a satisfactory signal-to-noise ratio and validating the suitability of the models for navigating the design space. The close agreement between adjusted R^2 and predicted R^2 values further supported the reliability and robustness of the statistical models.

Numerical optimization was performed using the desirability function approach, with the objective of minimizing particle size while maximizing drug entrapment efficiency and drug content, while maintaining the formulation variables within the selected experimental range.

Formulation of Microsponge-Loaded *In-Situ* Gel

The optimized microsponges were successfully incorporated into thermoresponsive *In-Situ* gel formulations using varying concentrations of polymer to obtain formulations ISG 1, ISG 2, and ISG 3. The formulations were prepared as clear, homogeneous sols at room temperature, which transformed into gels at physiological temperature. The incorporation of microsponges did not affect the clarity or homogeneity of the formulations, indicating uniform dispersion within the polymeric matrix.

Visual inspection

All the prepared formulations were visually inspected for clarity, homogeneity, and presence of particulate matter. The formulations (ISG 1, ISG 2, and ISG 3) appeared translucent, clear, and free from any visible aggregates or phase separation. This indicates the successful formulation of physically stable *In-Situ* gels with uniform distribution of microsponges.⁷

pH measurement

The pH of the prepared *In-Situ* gel formulations ranged from 4.98 ± 0.11 to 5.26 ± 0.09 . The results indicated no significant variation among the formulations. Although the ideal pH for ophthalmic preparations is around 7.2 ± 0.2 , the obtained pH range is acceptable for nasal administration and is unlikely to cause irritation. A slight increase in pH was observed with increasing concentration of Poloxamer, indicating its influence on formulation pH.^{8,9}

Rheological behavior (viscosity)

The viscosity of the formulations was evaluated at 30°C and found to be in the range of 3509–3699 cPs. The results demonstrated that viscosity increased with increasing concentration of the thermoresponsive polymer (Poloxamer). Adequate viscosity is essential for prolonging nasal residence time and enhancing drug absorption. Among the formulations, ISG 3 exhibited the highest viscosity, suggesting improved mucoadhesive potential and sustained drug release behavior.⁷

Gelation time

All formulations exhibited rapid gelation within the acceptable range for *In-Situ* nasal gels. The gelation time ranged from 29 ± 1.05 sec to 36 ± 2.65 sec. It was observed that an increase in polymer concentration resulted in a decrease in gelation time. Among the formulations, ISG 3 showed the shortest gelation time, indicating faster sol-to-gel transition, which is desirable for effective nasal retention.¹⁰

Gelation temperature

The gelation temperature of the formulations ranged from $28.7 \pm 0.22^\circ\text{C}$ to $33.2 \pm 0.14^\circ\text{C}$, which is suitable for

nasal drug delivery systems. A gelation temperature above 25°C ensures ease of handling, storage, and administration. It was observed that increasing polymer concentration decreased the gelation temperature. ISG 3 exhibited the lowest gelation temperature, making it the most suitable formulation for rapid gel formation at physiological conditions.⁸

In vitro drug release from gel

The *in vitro* drug release studies demonstrated sustained release of the drug from the microsponge-loaded *In-Situ* gel formulations. The optimized formulation (ISG 3) showed a high cumulative drug release, indicating effective diffusion of the drug from the microsponge matrix followed by release from the gel network. The controlled release behavior can be attributed to the combined effect of microsponges and the viscous gel matrix, which helps in prolonging drug release and improving therapeutic efficacy.^{7,8}

Release Kinetics

The *in vitro* drug release study demonstrated a sustained release profile, with cumulative drug release increasing from 6.09% at 30 min to 39.45% at 480 min. The dissolution data were fitted to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas kinetic models to elucidate the release mechanism. Among the models evaluated, the zero-order model showed the highest correlation coefficient ($R^2 = 0.9883$), indicating that the optimized formulation predominantly followed zero-order release kinetics. The Korsmeyer–Peppas model also exhibited a high correlation ($R^2 = 0.9831$), suggesting that diffusion contributed to the drug release process. Comparatively lower R^2 values were obtained for the Hixson–Crowell (0.9645), first-order (0.9471), and Higuchi (0.9309) models. Overall, the findings indicate that the formulation provided a controlled and sustained drug release profile, with zero-order kinetics best describing the release behavior.

Short-term stability studies

Short-term stability studies of the optimized formulation (ISG 3) were conducted as per ICH guidelines at 25°C/60% RH and 30°C/65% RH for 3 months. The formulation remained physically stable throughout the study period, with no significant changes in appearance, texture, or pH. The gelation time showed a slight increase from 32 sec to 40 sec over 90 days, which remained within acceptable limits. The pH values varied minimally between 4.86 and 5.19. Drug content showed a marginal decrease from 98% to 96%, while dissolution remained above 97%. No precipitation or syneresis was observed, indicating good stability of the formulation. These results confirm that the optimized formulation maintains its integrity and performance over time.^{9,10}

CONCLUSION

The present study successfully developed and optimized sumatriptan succinate-loaded microsponges incorporated into a thermosensitive *In-Situ* nasal gel system for potential application in migraine therapy. Microsponges prepared by the quasi-emulsion solvent diffusion technique exhibited suitable particle size, satisfactory drug loading, and a porous morphology capable of sustaining drug release. The factorial design approach effectively identified the influence of polymer concentration and stirring speed on the critical quality attributes of the formulation. The optimized formulation demonstrated appropriate particle size, high entrapment efficiency, and sustained drug release characteristics. Incorporation of the optimized microsponges into a Poloxamer-based *In-Situ* nasal gel is expected to enhance nasal residence time and facilitate controlled drug delivery to the systemic circulation and potentially the brain. Overall, the developed formulation represents a promising strategy for improving the therapeutic efficacy and patient compliance of sumatriptan succinate in migraine management. Further *in vivo* and pharmacokinetic studies can be performed to confirm the clinical potential of the developed microsponge-based intranasal delivery system.

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