Formulation and Evaluation of Intranasal Drug Delivery System of Sumatriptan Succinate

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***Abstract*—Migraine is a chronic neurological disorder characterized by recurrent attacks of severe headache accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia. Sumatriptan succinate, a selective serotonin (5-HT$_1$B/5-HT$_1$D) receptor agonist, is commonly used for the acute treatment of migraine. However, its oral administration is associated with low bioavailability due to extensive first-pass metabolism and delayed onset of action. The present study aims to formulate and evaluate an intranasal drug delivery system of sumatriptan succinate to enhance bioavailability and provide rapid therapeutic action. Intranasal formulations were prepared using suitable polymers and excipients to improve nasal residence time and drug permeation. The prepared formulations were evaluated for physicochemical characteristics such as pH, drug content, viscosity, and in vitro drug release. Ex vivo permeation and stability studies were also carried out. The results indicated that the intranasal formulation showed rapid drug release and improved permeation, suggesting that intranasal delivery of sumatriptan succinate is a promising alternative to conventional oral dosage forms for effective migraine management.**

***Keywords*—Sumatriptan succinate, Intranasal drug delivery system, Migraine, Bioavailability, Nasal formulation, In vitro evaluation**

I. INTRODUCTION

Migraine is a chronic, disabling neurological disorder characterized by recurrent attacks of moderate to severe headache, typically unilateral, and often associated with nausea, vomiting, photophobia, and phonophobia. It affects a substantial portion of the global population and is considered one of the leading causes of disability, particularly among young and middle-aged adults. The pathophysiology of migraine involves complex neurovascular mechanisms, including trigeminovascular system activation, release of vasoactive neuropeptides, and dilation of intracranial blood vessels.

Pharmacological management of migraine primarily focuses on providing rapid relief from acute attacks and preventing recurrence. Among the various antimigraine agents, triptans represent the most effective class of drugs for the acute treatment of migraine. Sumatriptan succinate, the first drug of this class, is a selective serotonin (5-HT$_1$B/5-HT$_1$D) receptor agonist that exerts its therapeutic effect by causing vasoconstriction of cranial blood vessels, inhibiting the release of inflammatory neuropeptides, and blocking pain signal transmission in the trigeminal nerve pathway.

Despite its proven efficacy, oral administration of sumatriptan succinate presents several limitations. The drug exhibits low oral bioavailability (approximately 15%) due to extensive first-pass hepatic metabolism. Furthermore, migraine attacks are often accompanied by gastrointestinal disturbances such as nausea, vomiting, and delayed gastric emptying, which can further compromise drug absorption and delay onset of action. Although subcutaneous and intravenous routes provide rapid relief, they are invasive, may cause discomfort, and are associated with poor patient compliance.

In recent years, the intranasal route has emerged as a promising alternative for systemic drug delivery, particularly for drugs requiring rapid onset of action. The nasal cavity offers several advantages, including a large surface area, high permeability, rich vascularization, and avoidance of hepatic first-pass metabolism. Intranasal drug delivery also provides faster absorption compared to oral dosage forms and is especially beneficial for patients who are unable to tolerate oral medications during migraine attacks.

However, the intranasal route also presents challenges such as limited nasal residence time due to mucociliary clearance and enzymatic degradation. To overcome these limitations, formulation strategies such as the use of mucoadhesive

polymers, absorption enhancers, and optimized viscosity systems are employed to enhance drug retention, permeation, and bioavailability.

The present study aims to formulate and evaluate an intranasal drug delivery system of sumatriptan succinate to achieve rapid drug absorption, enhanced bioavailability, and improved therapeutic efficacy. By selecting suitable excipients and evaluating the formulation for physicochemical properties, in vitro drug release, ex vivo permeation, and stability, this research seeks to develop a patient-friendly and effective alternative to conventional dosage forms for the management of acute migraine attacks

II. MATERIALS AND METHODS

Materials

Sumatriptan succinate was obtained as a gift sample from a reputed pharmaceutical company and used as received. Chitosan and Carbopol 934P were selected as mucoadhesive polymers for intranasal delivery. Benzalkonium chloride was used as a preservative, while sodium chloride was incorporated to maintain isotonicity of the formulation. Sodium hydroxide and hydrochloric acid were used for pH adjustment. All chemicals and reagents employed in the study were of analytical grade. Distilled water was used throughout the experimental work.

Preformulation Studies

The drug was evaluated for its organoleptic properties such as color, odor, and physical appearance by visual inspection. Solubility studies of sumatriptan succinate were performed in distilled water and phosphate buffer (pH 6.4) using the shake-flask method to assess its suitability for intranasal delivery. The maximum absorbance (λmax) of the drug was determined using a UV–Visible spectrophotometer by scanning the drug solution in the range of 200–400 nm.

Drug–polymer compatibility was evaluated by Fourier Transform Infrared (FTIR) spectroscopy. FTIR spectra of pure sumatriptan succinate and physical mixtures of the drug with selected polymers were recorded and compared to identify any possible chemical interactions.

Formulation of Intranasal Drug Delivery System

Intranasal formulations of sumatriptan succinate were prepared using the cold method. Accurately weighed quantities of the selected polymer were gradually dispersed in distilled water with continuous magnetic stirring and allowed to hydrate completely to form a uniform polymeric dispersion. Sumatriptan succinate was dissolved separately in distilled water and slowly added to the polymer dispersion under constant stirring to ensure homogeneity.

Benzalkonium chloride was added as a preservative, and sodium chloride was incorporated to achieve isotonicity. The pH of the formulation was adjusted to the range of 5.5–6.5 using 0.1 N sodium hydroxide or hydrochloric acid, which is considered suitable for nasal administration. The final volume was adjusted with distilled water, and the prepared formulations were stored in sterile, tightly closed containers for further evaluation.

Evaluation of Intranasal Formulations

Physical Appearance and pH

All formulations were visually examined for clarity, color, and the presence of any particulate matter. The pH of the formulations was measured using a calibrated digital pH meter at room temperature.

Drug Content

Drug content uniformity was determined by diluting a known volume of the formulation with phosphate buffer (pH 6.4). The solution was analyzed using a UV–Visible spectrophotometer at the predetermined λmax, and the drug content was calculated.

Viscosity

The viscosity of the intranasal formulations was measured using a Brookfield viscometer at appropriate spindle speed to ensure acceptable flow properties for nasal administration.

Mucoadhesive Strength

Mucoadhesive strength was evaluated using freshly excised nasal mucosa mounted on a modified balance apparatus. The force required to detach the formulation from the mucosal surface was measured and expressed as mucoadhesive strength.

In Vitro Drug Diffusion Study

In vitro drug diffusion studies were carried out using a Franz diffusion cell. A dialysis membrane (or excised nasal mucosa) was mounted between the donor and receptor compartments. Phosphate buffer

(pH 6.4) was used as the receptor medium and maintained at 37 ± 0.5 °C with continuous stirring. Samples were withdrawn at predetermined time intervals, replaced with fresh buffer, and analyzed spectrophotometrically. The cumulative percentage of drug diffused was calculated.

Release Kinetic Study

The in vitro diffusion data were fitted to different kinetic models, including zero-order, first-order, and Higuchi models, to understand the drug release behavior and mechanism.

Fourier-Transform Infrared Spectroscopy (FTIR):

1. IR spectral analysis Infrared

(IR) spectroscopy was employed to identify functional groups and molecular structures of the synthesized compounds. The sample was prepared by grinding 1–2 mg of the solid sample with 100 mg of dry KBr powder (Sigma-Aldrich, FTIR grade), which was then compressed into a thin, transparent pellet using a hydraulic press (PerkinElmer, model 25T). For liquid samples, a thin film was applied onto an ATR crystal (PerkinElmer, Diamond/ZnSe) or between two KBr discs (Sigma-Aldrich). The FTIR spectrometer (PerkinElmer Spectrum Two) was set to a resolution of 4 cm^{-1}, and the background spectrum was collected before sample measurement. The IR spectrum was analyzed in the range of 4000–400 cm^{-1} to identify characteristic absorption bands corresponding to functional groups such as hydroxyl (-OH), carbonyl (-C=O), and amines (-NH2).

III. RESULTS AND DISCUSSION

DESIGN AND EVALUATION OF SUMATRIPTAN SUCCINATE MUCOADHESIVE *IN-SITU* GEL

Differential scanning calorimetry (DSC)

A thermogram of DSC highlights certain thermal parameters on the basis of which we can understand physical nature of substance and its identity. The area of a peak is in direct relation to the energy change of a sample. A DSC thermograph of sumatriptan succinate as in Figure 1.1 shows sharp endothermic peak at temperature of 173.27^{0}C. This peak is due to the melting of Sumatriptan succinate. From this thermograph, the identity of sumatriptan succinate was confirmed through its melting point.

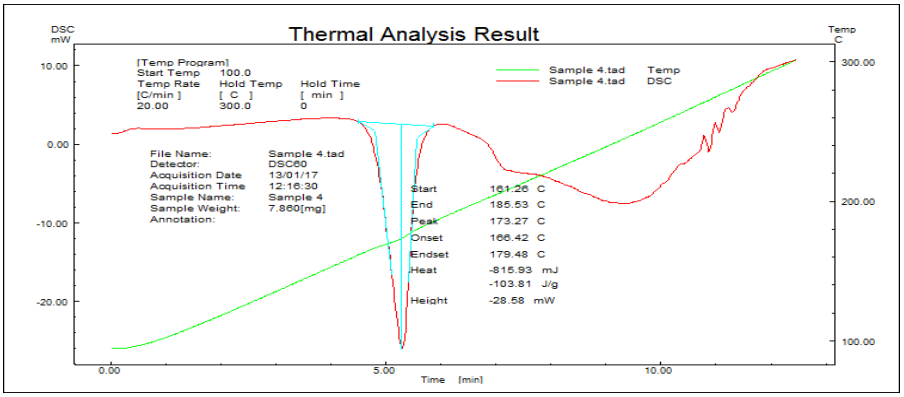

Fig1.1Thermogram of differential scanning calorimetry of Sumatriptan succinate

Identification and compatibility study by FTIR

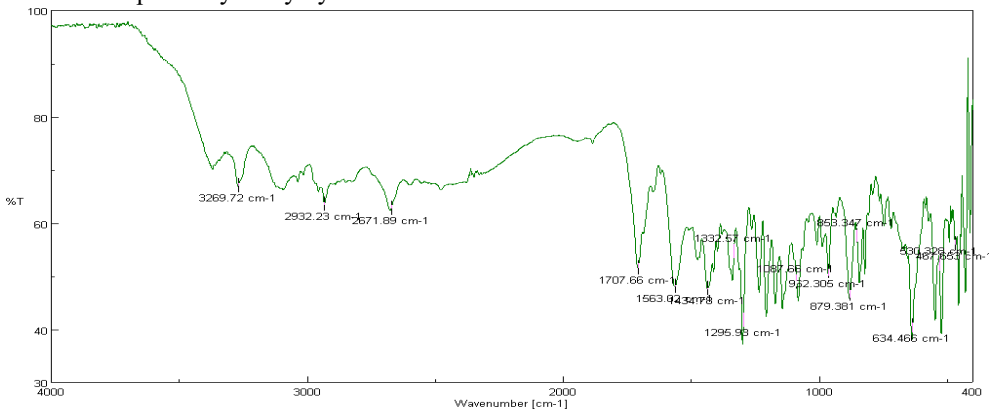

Fig1.2 FTIR spectrum showing identification of functional groups of Sumatriptan Succinate

Table1.1Identificationoffunctionalgroupscomparedwith Standard valuesof sumatriptan succinate

S No	Wavelength(cm^{-1})	Range	Functional group
1	1139.88	1100-1300	OH
2	1205.73	1250-1030	[CH3]-N
3	1343.41	1350-1140	Sulphonamide
4	1565.64	1500-1600	Aromaticring [-C=C-]
5	1708.11	1680-1760	CH=0
6	2931.35	2850-2960	Alkane [CH3]
7	3104.20	3000-3100	Aromatic ring [CH]
8	3376.44	3500-3200	NH-

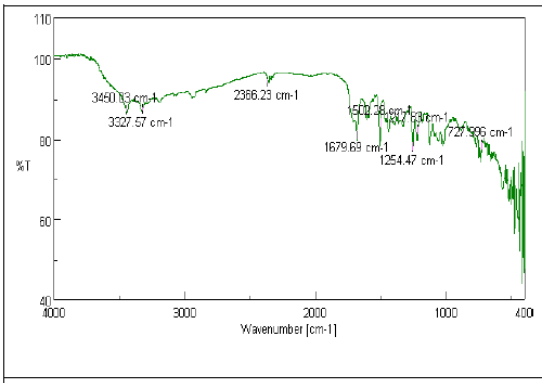

Fig1.3FTIR spectrum of sumatriptan succinate + ellangum

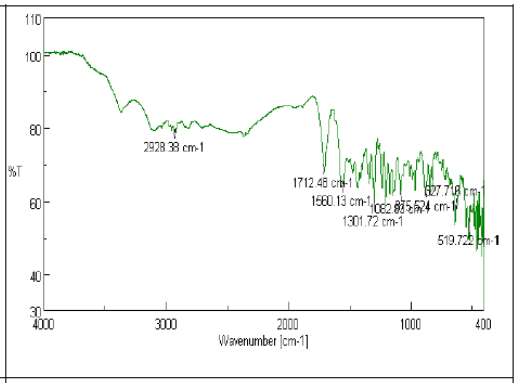

Fig1.4FTIR spectrum of sumatriptan succinate+physical mixture (gellangum+ PEG 400+ mannitol)

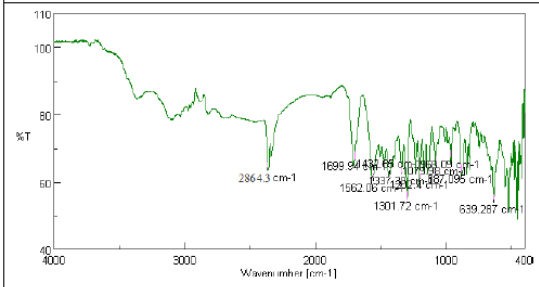

Fig 1.5 FTIR spectrum of gellangum+ KCl

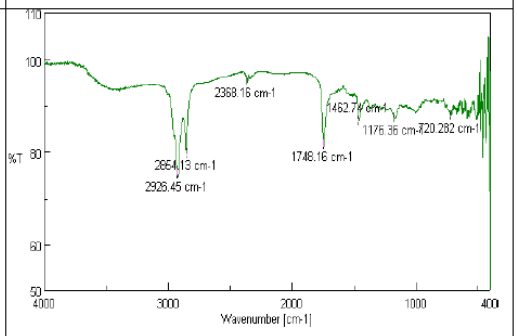

Fig1.6 FTIRspectrumofgellangum+ CaCl2

Optimization of working concentration of gellan gum

Numerous concentrations of gellan gum 0.1 to 0.5 % w/v serially were reviewedtofix lowestpossibleconcentration toobtain ion activated *in-situ* gel at temp of 32°C to 34°C (temp of nasal cavity) with minimum possibleviscosity.Hence,0.2%w/vofgellangumwascar efully chosen for further studies.

Plotting calibration curve for Sumatriptan succinate in PB pH 6.4

Sumatriptan succinate solution was screened for spectrum measurement through 400-200 nm. After scanning, stock solution of sumatriptan succinate showed absorption region at 226.8 nm. The linearity in the calibration curve was observed from 1 to 7 µg/ml. Beers- Lambert's law was obeyed in this range. The R2 was 0.9992. This signifyes the best proportionality for absorbance vsconcentration. An equation Y=0.1359X + 0.0137 indicates 0.1359 intercept and 0.0137 constant. See Figure 1.7

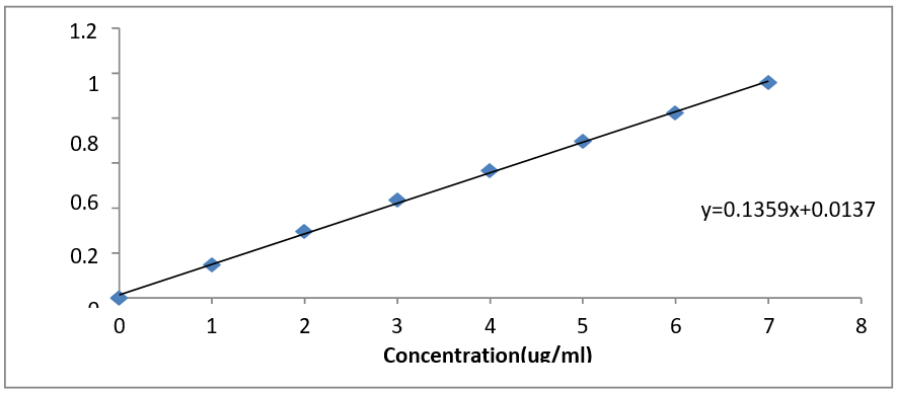

Fig1.7 Plot of calibration curve for Sumatriptan succinate

In-vitro drug release

Diffusion study was conducted for all formulations utilizing PB pH 6.4 as diffusion medium. The data of this study is presented in Table 7.5. The release rate depends on gellan gum concentration. Drug release slows down with higher gellan gum concentration. The formulation F7 showed 98.57 % release of sumatriptan at the end of 5 h. Figure 7.9 exhibits the drug release for all formulations after 5 h was near to 90%.

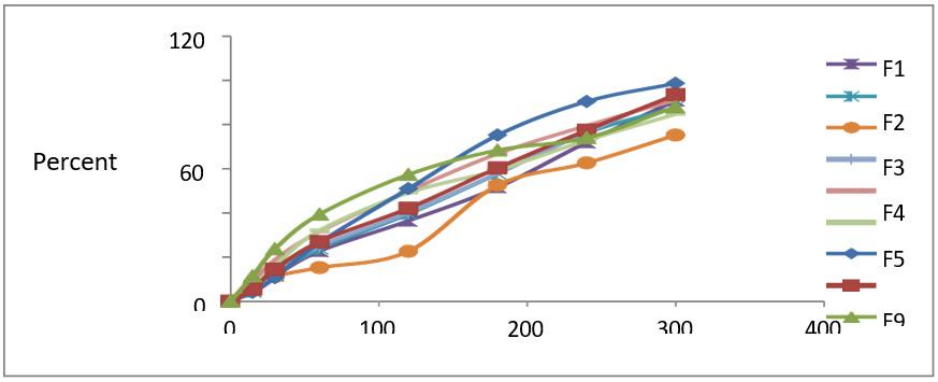

Fig1.8 *In-vitro* drug release profile of factorial batch esof*in-situ* gel

IV. CONCLUSION

The current study was intended to design and develop mucoadhesive compositions of some drugs for nasal delivery. Mucoadhesive formulations are meaningful to improve contact time with mucosa and in so doing enhancing the uptake of drug. In this study sumatriptan succinate in-situ gel was the drug of choice for brain delivery. There is a great suitability of sumatriptan succinate to operate it nasally to upgrade bioavailability by circumventing hepatic degradation. Mucoadhesive in-situ gel was settled by using deacetylated gellan gum as a gelling agent.A simulated nasal fluid was used to study in vitro. In-vivo study of optimized batch was demonstrated on Sprague Dawly rats. Sumatriptan was scrutinised in plasma by UPLC-MS. The optimum batch showed sumatriptan release 98.57% at the end of 5 h which obeys Peppas model of drug release. In ex-vivo study, 93.33% diffusion was observed in 5 h. Also the safety of optimum batch had been demonstrated in histopathology study. DTI for brain tissues was realized at 1.866.

The present research work is therefore evidence based and has satisfied the proposed aim and objectives.

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