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DEVELOPMENT OF A FAST-ACTING NANOSUSPENSION NASAL DROP USING A NOVEL CO-PROCESSED POLYMER FOR MIGRAINE RELIEF

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ABSTRACT
Background: Effective central nervous system (CNS) drug delivery remains challenging due to the blood-brain barrier. Nasal drug delivery offers a non-invasive alternative, ensuring rapid drug absorption and onset of action. Prochlorperazine Maleate, a drug for migraines, suffers from poor solubility, limiting its therapeutic potential. **Methodology:** A nanosuspension-based nasal drop was developed and optimized using high-pressure homogenization. A novel co-processed polymer enhances solubility and stability. Key formulation parameters, including particle size, zeta potential, and polymer concentration, were optimized using a central composite design. The optimized nanosuspension was characterized for its physicochemical properties, drug release, and stability. **Results and Discussion:** The optimized formulation (Batch F9) exhibited a particle size of 78.8 nm and a high drug release rate (93.87% in 8 hours). Stability studies confirmed no significant changes in drug content, pH, or osmolality over a three-month period. The nasal drop provided consistent dosing, with each actuation delivering a precise amount of drug content. In vitro drug release studies demonstrated a sustained release pattern, enabling prolonged migraine relief. **Conclusion:** The developed nanosuspension nasal drop presents a promising solution for CNS drug delivery, ensuring rapid and sustained therapeutic outcomes. This nanosuspension nasal drop achieved a 5.6-fold enhancement in solubility and demonstrated rapid onset within 10 minutes post-administration. Although promising, the study is limited to in vitro characterization; future research should explore in vivo efficacy and long-term safety.

INTRODUCTION

The central nervous system (CNS), comprising the brain and spinal cord, is the primary network that regulates and maintains essential bodily functions. Neurological disorders affecting the CNS present a significant global health challenge, impacting over 100 million people worldwide and often requiring prolonged and complex treatment regimens, as highlighted by the World Health Organization (WHO) [1]. However, effective drug delivery to the CNS remains a critical hurdle, primarily due to the restrictive nature of the blood-brain barrier (BBB). This specialized, semipermeable membrane serves as a protective shield, preventing the majority of small-molecule drugs and nearly all large biomolecules from entering the brain [2]. The BBB, along with the blood-cerebrospinal fluid barrier (BCSFB)

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and the blood-tumor barrier, limits the movement of therapeutic agents into the CNS. These barriers impose stringent controls over the exchange of molecules, blocking the entry of toxins and, unfortunately, essential medications. Additionally, efflux transporter proteins, such as breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), and multidrug resistance protein (MRP), act as gatekeepers, actively expelling drugs from the brain's capillary endothelium and further reducing drug efficacy [3]. Strategies to overcome these challenges have been extensively studied, including targeting efflux mechanisms and employing advanced transcytosis processes to facilitate drug penetration into the CNS. Previous studies have investigated the intranasal delivery of Prochlorperazine Maleate for CNS applications. For instance, Kaur et al. (2023) reported enhanced absorption via the nasal mucosa. Recent advancements in nanosuspension delivery systems (Patel et al., 2021) and co-processed polymers, particularly those incorporating HPMC and mannitol matrices (Parmar et al., 2021), have demonstrated improved stability and bioavailability [4-6].

Neurological disorders like migraine represent a significant unmet medical need. Migraine, a complex neurobiological condition characterized by heightened CNS excitability, manifests through severe episodic headaches accompanied by symptoms such as nausea, vomiting, and unilateral pain. The WHO recognizes severe migraines as among the most disabling chronic disorders, affecting daily life and productivity for millions worldwide [4].

Oral administration remains a popular method for drug delivery due to its convenience, but it often suffers from drawbacks like poor bioavailability, first-pass metabolism, and systemic side effects. Alternative delivery routes, including nasal, pulmonary, and transdermal methods, have been explored to overcome these limitations. Among these, nasal drug delivery has emerged as a promising strategy, offering a rapid and non-invasive route to bypass the gastrointestinal tract and first-pass hepatic metabolism [5].

The nasal cavity, divided by the nasal septum, serves not only as a respiratory and olfactory organ but also as a highly vascularized site for drug absorption. Drugs administered intranasally can be deposited in three central regions, with the potential to reach the CNS directly through pathways such as the olfactory and trigeminal nerve routes. These neural connections provide a direct and efficient route for drug molecules to enter the cerebrospinal fluid (CSF), offering a unique advantage over traditional systemic administration [6].

The first barrier to nasal drug absorption is the mucus layer, which can hinder the diffusion of large, charged molecules while allowing smaller, unmodified drugs to pass more freely. Mucin, the primary glycoprotein in mucus, binds to solutes, thereby influencing the diffusion and absorption of drugs. Environmental factors, such as pH and temperature, can further modify the properties of the mucus layer, thereby impacting drug permeability. While the exact mechanisms of CNS drug delivery through the nasal route are still being elucidated, current research underscores the significance of the olfactory and trigeminal nerve pathways in facilitating direct transport to the brain [7].

Intranasal administration has proven beneficial for delivering low-dose medications with poor oral bioavailability, particularly for proteins, peptides, and treatments for CNS disorders. The nasal route offers the advantages of high patient compliance, ease of self-administration, and a large absorptive surface area due to the highly vascularized nasal mucosa. These attributes make nasal delivery an appealing strategy for treating CNS diseases like depression, epilepsy, and Alzheimer's disease, where conventional systemic approaches face significant obstacles [8].

For drugs classified under the Biopharmaceutics Classification System (BCS) Class II, limited water solubility significantly impedes oral bioavailability. Traditional approaches, such as the use of organic solvents, solid dispersions, and cyclodextrin complexes, have been employed to enhance the dissolution rates of drugs. However, nanosuspension technology, which reduces particle size to the nanometer range, provides a more effective solution by increasing the surface area and improving drug solubility and stability [9].

Nasal drop formulations represent an innovative and non-invasive method for rapid drug delivery, offering significant advantages in terms of ease of use, portability, and cost-effectiveness. These formulations have shown high patient compliance and the potential for self-administration, making them suitable for acute treatments, such as migraine relief. By leveraging the benefits of nanotechnology, nasal drops can

deliver drugs efficiently, enhancing their therapeutic efficacy & opening new avenues for treating CNS-related conditions [10]. Despite these advancements, limited studies have explored the integration of co-processed polymers designed explicitly for nasal nanosuspensions of Prochlorperazine Maleate. This study addresses this gap by formulating a fast-acting nasal drop using a novel co-processed polymer to enhance solubility, stability, and CNS-targeted drug delivery.

MATERIAL AND METHODS

Materials

The materials used in this research included Prochlorperazine Maleate from Sisco Research Laboratories (SRL), India; Carboxy Methyl Cellulose (CMC) from Sigma-Aldrich, USA; Sodium Citrate from Merck, Germany; Glycerol from Fischer Scientific, India; Tween 40 from Loba Chemie, India; Methanol from Rankem, India; Hydrochloric Acid (HCl) from Thermo Fisher Scientific, India; Sodium Chloride from Qualigens, India; Ethylenediaminetetraacetic acid (EDTA) from Himedia, India; and Benzalkonium Chloride from Loba Chemie, India.

Methods

Preformulation & Formulation Studies of Prochlorperazine Maleate

Preformulation Studies

Melting point

The melting point was determined using the capillary method. The capillary tube was sealed at one end, and the drug was filled inside the capillary tube from the other end. It was then tied to a thermometer. The thermometer, along with the capillary, was inserted into the melting point apparatus, and the tube was heated. The temperature at which the drug begins to melt is recorded as its melting point.

Identification by FTIR

FT-IR was performed by using a Bruker FT-IR ALPHA II instrument to identify the obtained Prochlorperazine Maleate. The Prochlorperazine Maleate sample was mixed with KBr and crushed using a mortar and pestle. The mixture was then analysed by using the instrument, and a graph was obtained.

Particle Size Analysis & Zeta Potential

The sample is diluted in proportions of 1:10, 1:30, 1:100, or 1:200 with alcohol. The solution was subjected to sonication for 10 minutes and subsequently passed through a Whatman filter paper for filtration. The filtrate is collected for analysis. The laser light source produces illumination that penetrates the sample within the cell. At 90° (right angle) or 173° (back angle), one of the two detectors collects the scattered light signal. Two detectors provide more flexibility in measurement conditions. Several liquids can disperse particles. For measurement interpretation, only the liquid refractive index & viscosity are required.

Development of a drug's calibration curve

A calibration curve for Prochlorperazine was created by graphing the relationship between absorbance and concentration (µg/ml). A range of dilutions was made, starting from 5 to 25 µg/ml, using phosphate buffer at pH 6.8. Samples were generated and analysed for absorbance at a wavelength of 258 nm [11].

Drug Excipients Compatibility Studies

Compatibility between Prochlorperazine Maleate and excipients (Carboxymethyl Cellulose, Sodium Citrate, Glycerol, and Tween 40) was evaluated using FTIR and UV spectrophotometry to ensure that no interactions occurred that could affect the formulation.

X-Ray Diffraction (XRD)

The crystalline properties of Prochlorperazine Maleate were analyzed using an XRD instrument (Ultima-IV), operated at 40 kV/40 mA. The sample was placed on a glass slide and scanned continuously in 2Theta/Theta mode.

Thermo gravimetric analysis

Differential Scanning Calorimetry (DSC) was performed using a Mettler Toledo STARe system. A sample weighing 1.3 mg was heated from 25°C to 300°C at a rate of 10°C/min in an aluminum pan under a nitrogen atmosphere (20 mL/min).

Preparation of Nanosuspension

Prochlorperazine Maleate was dissolved in methanol to prepare an organic solution. The aqueous phase was prepared by dissolving Carboxymethyl Cellulose (CMC), Tween 40 (as a surfactant), and Sodium Citrate (as a preservative) in a mixture of glycerol and water. The organic solution was slowly added to the aqueous phase at room temperature, using a high-pressure homogenizer running at 11,000 rpm for 2 hours. Methanol was evaporated during this process to form a stable nanosuspension.

The homogenization speed and time (11,000 rpm for 2 hours) were optimized based on preliminary trials assessing particle size and polydispersity index (PDI). Beyond 2 hours, no significant reduction in particle size was observed [12-13].

EXPERIMENTAL DESIGN AND FORMULATION

To optimize the nanosuspension, a high-pressure homogenization method was employed, utilizing a Central Composite Design (CCD) with three factors: A, homogenization speed; B, Tween 40 concentration; and C, CMC concentration. These variables were tested at high (+1) and low (-1) levels, with particle size as the dependent variable. The design included 13 experimental runs conducted randomly, and each formulation was tested for its properties and stability [14].

ASSESSMENT OF NANOSUSPENSION

Appearance: Nanosuspension appearance is visually observed.

Resolvability: The resolvability or redispersibility of nanosuspension was evaluated by manually tilting the vials containing nanosuspension back and forth until the sediment was uniformly dispersed in the aqueous phase. It was noted how many tilts were there.

Viscosity: The Nanosuspension was prepared using a Brookfield viscometer with the spindle No. 60 set at a speed of 100 rpm.

Saturation solubility study: The saturation solubility of the formulated nanosuspension was determined by placing it in a vial and stirring it for 48 hours using a magnetic stirrer set at 100 RPM to achieve saturation. Next, 2 milliliters of nanosuspension were placed into an Eppendorf tube and subjected to centrifugation at 10,000 rpm for 30 minutes. Liquid portion passed via 0.2μm syringe filter & examined applying UV-visible spectrophotometer [UV-1800, Shimadzu, Japan] at wavelength where the drug absorbs the most of the light, after appropriately diluting it with the same liquid used as a reference.

Assay: A 1ml portion of nanosuspension contains 2mg of medication. This was diluted with 100 mL of methanol and filtered using a 0.2 μm filter. By using the UV spectrophotometer of the API's maximum wavelength (λmax), the total content was determined. A standard solution with a comparable concentration was created, then the standard solution absorbance was utilized for computing the percentage of the Assay using the following formula:

$$\%\ \boldsymbol{Assay} = \frac{\boldsymbol{Sample\ absorbance}}{\boldsymbol{Standard\ absorbance}} \times \mathbf{100}$$

Particle Size

A Malvern Zetasizer Nano ZS90 is used for determining the particle size of nanosuspensions. The Zetasizer utilises the light diffraction method known as PCS (Photon Correlation Spectroscopy) to measure the mean particle size of the produced nanosuspension. To get a scattering intensity suitable for examination, the test samples are diluted with water. Before being measured, the samples were shaken to re-disperse them.

Zeta-Potential

The zeta-potential quantitatively measures the electric charge on particle surfaces, indicating the physical stability of colloidal dispersions. Aqueous dispersions exhibiting zeta potential levels that exceed |30mV| demonstrate extended electrostatic stability. Using a Zetasizer to measure the particles' electrophoretic mobility, this study assessed the Zeta Potential.

In-vitro Drug release

The complete preparations involve the use of USP category II dissolution equipment. The dissolution medium consists of 900 mL of pH 6.8 Phosphate Buffer, and the rotation speed is set at 50 rpm. The temperature is maintained at a constant value of 37 ± 0.5 °C. Sampling was conducted at programmed time intervals ranging from 0.5 to 12 hours.

Aliquot samples of 5ml were obtained and then replaced with an equal amount of fresh medium. A membrane filter paper with a pore size of 0.45 μm was used to filter a 5 mL aliquot sample. A UV-Vis spectrophotometer was used to measure the absorbance of the resultant filtrate after it had been suitably diluted with fresh medium.

Stability Testing of the Optimized Nanosuspension

The improved nanosuspension underwent stability research in a stability chamber for 3 months at a temperature of 40˚ ± 2˚C and 70% ± 5% relative humidity. The samples were assessed monthly for drug content [15].

Preparation of Nasal Drops

The finished batch of Nanosuspension was utilized to prepare the Nasal Drop of Prochlorperazine Maleate. Begin by measuring the precise amount of Tonicity Modifier (Sodium Chloride) and Chelating agent (EDTA) and placing them in a

container. Next, add the exact quantity of the completed Nanosuspension (API) to the container and thoroughly mix the ingredients. Next, include the precise amount of Preservative (Benzylkonium Chloride) into the prepared mixture, ensuring accuracy. Thoroughly blend the ingredients using an overhead mixer. Set the capacity to 10 milliliters by adding water. To achieve a pH of 5.5, the solution was made less acidic by diluting hydrochloric acid (HCl). The nasal drop was created using this method, and it should be filled into a suitable container [16].

EVALUATION OF NASAL DROP

Clarity: The clarity of the formulation was visually observed against a white and black background as a clear solution, a viscous solution, or a turbid solution.

pH: The nasal drop formulation pH was determined using a digital pH-meter (Thermoscientific, Orion StarA211). The pH of the formulation was calculated as the mean of three readings. It is essential for assessing the apparent pH of both the solution and the suspension of nasal drops and creating a suitable acceptance criterion. Lysozyme is present in nasal secretions and plays a role in eliminating certain bacteria in acidic environments.

In alkaline conditions, lysozyme is rendered inactive, rendering the nasal tissue vulnerable to microbial infection. The pH of the final nasal drop formulation was adjusted to 5.5 using 0.1 N hydrochloric acid (HCl), with continuous stirring, and monitored using a calibrated digital pH meter. This is because drugs are absorbed more effectively in their un-ionized state.

Osmolality: The manufacturer should test and control the osmolality of the formulation using a suitable process and establish an acceptable criterion. Animal studies have demonstrated that nasal drop formulations of salmon calcitonin with an osmolality of 100 or 600 mOsmol/Kg have higher bioavailability compared to isotonic formulations.

Additional research has shown that hypotonic nasal drop formulations enhance the capacity of drugs to pass through the nasal mucosa. Several currently available products have documented osmolality levels ranging from 300 to 700 mOsmol/Kg. Using an Osmometer (Freezing Point Osmometer), the osmolality of the nasal drop was derived. The procedure is given below:

1. The sample to be tested was filled into the osmometer.
2. The analysis starts as soon as the sampler tip is placed into the instrument's sample port.
3. The osmolality of the sample was noted.
4. Once the test is finished, the sampler is removed from the osmometer and then discarded. The sampler & sample chamber were appropriately cleaned.

Actuations per container

The term "actuation" describes the release process of a medication from a drug delivery device, typically triggered by a single activation, such as an exhale or a mechanical action. Actuations were verified by tallying the overall number of activations until the canister's contents were fully depleted. These characteristics include stroke length (the distance in millimeters that the drop device is compressed), velocity (or force), and compression acceleration. Actuation parameters vary amongst different patient demographics, such as youthful, adult, or older individuals. Hence, it is crucial to establish accurate actuation parameters for a specific device as well as the intended patient demographic.

Drug Amount (content) per actuation

Wavelength at 258nm, employing a UV-spectrophotometer, the amount of medicine delivered per drop, and the average of six actuations were examined to ensure that it complied with the claims on the label. Ten deliveries were made below the MDI methanol's surface in a beaker containing 75 mL of methanol. The container was shaken thoroughly each time, with a 5-second pause between drops.

Drug Content (Assay)

Analyze the drug material concentration throughout the entire container using a stability-indicating approach. This test ensures the reliability of manufacturing processes, such as formulation, filling, and sealing. The drug concentration of the nasal formulation was determined using a 258 nm UV-spectrophotometry calibration curve. Distilled water was used as a reference to measure the absorbance at 258 nm for the formulation sample. The average of three values is utilized as the drug content of the sample.

Stability study of optimized formulation

Stability research of Prochlorperazine nasal drop formulation conducted at 25±2˚C temperature & 60±5% relative humidity for 3 3-month duration. Samples underwent testing to assess

their clarity, pH level, osmolality, and number of actuations per container, as well as drug content per actuation and percentage assay after the designated storage period [17].

RESULTS AND DISCUSSION

Preliminary Analysis of Prochlorperazine Maleate

A preliminary examination of Prochlorperazine Maleate revealed the following physical and chemical characteristics. The drug was found to be a white, odorless powder. Solubility tests showed high solubility in methanol, moderate solubility in DMSO, and sparing solubility in water.

This initial solubility profile is crucial for formulating an effective drug delivery system, as it influences the selection of solvents and excipients (Table 1).

Table 1: Preliminary Analysis of Prochlorperazine Maleate

SN	Characteristics	Prochlorperazine Maleate
1.	**Description**	White coloured powder, odourless.
2.	**Solubility**	Prochlorperazine Maleate is soluble in Methanol, soluble in DMSO, and in inorganic solvents like buffers, and sparingly soluble in water.

Preformulation Studies

Melting Point of Prochlorperazine Maleate

The melting point was determined to be 207°C using the capillary method. This value aligns with the reference standards, confirming the drug's purity and consistency.

FTIR Analysis

FTIR spectroscopy was used to confirm the chemical structure of Prochlorperazine Maleate (Figure 1). Characteristic absorption peaks were observed: 3299 cm^{-1} (OH group of acid), 1735 & 1663 cm^{-1} (C=O groups), 2970 & 2953 cm^{-1} (aromatic CH stretching), and 2938 & 2917 cm^{-1} (aliphatic CH stretching). These peaks confirm the presence of functional groups consistent with the drug's molecular structure.

Particle Size Analysis

The average particle size of the pure drug, measured using a HORIBA Scientific SZ-100, was 183.1 nm, indicating a micronized form suitable for nanosuspension formulation (Figure 2). Reducing particle size enhances dissolution and bioavailability, making this an essential parameter for CNS drug delivery.

Zeta Potential

The Zeta potential of the pure drug was found to be -43.3 mV (Figure 3). This negative charge indicates good physical stability of the drug particles, as higher absolute values of zeta potential generally correlate with greater stability in suspension. The zeta potential of -43.3 mV suggests strong electrostatic repulsion between particles, minimizing aggregation. Values beyond ±30 mV are typically considered indicative of stable colloidal systems.

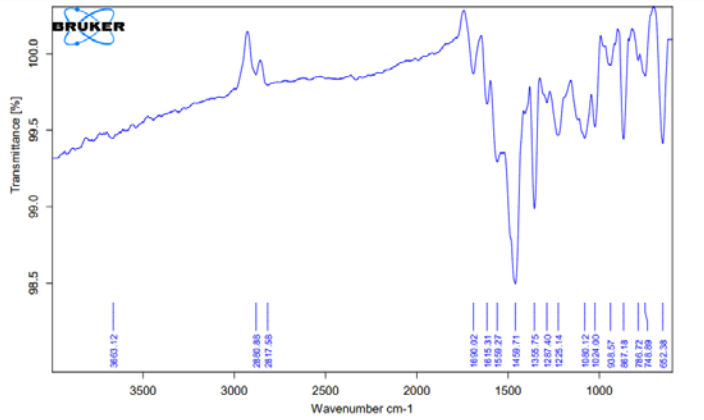

Figure 1: FTIR analysis of Prochlorperazine Maleate

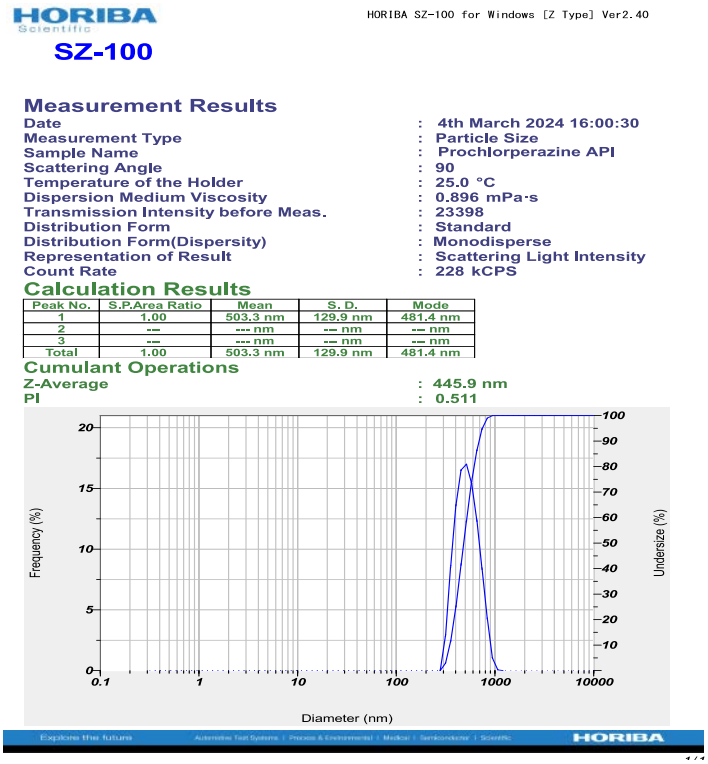

Figure 2: Particle Size Analysis of Prochlorperazine Maleate

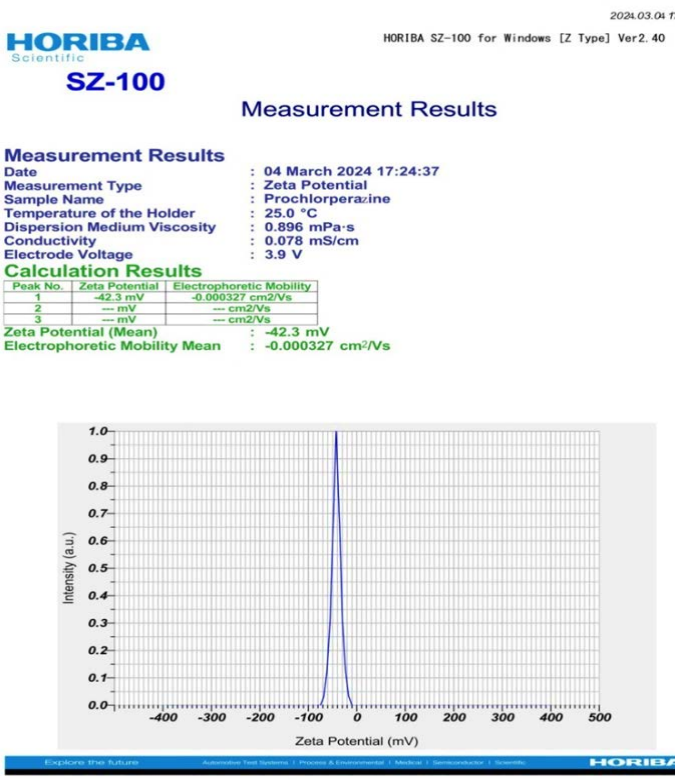

Figure 3: Zeta Potential Analysis of Prochlorperazine Maleate

Drug-Excipients Compatibility Studies

FTIR compatibility studies with excipients such as Carboxymethyl Cellulose, Sodium Citrate, Glycerol, and Tween 40 showed no significant shifts in the characteristic peaks of Prochlorperazine Maleate, indicating no chemical interaction between the drug and the excipients. This ensures the stability and efficacy of the drug-excipient combination in the formulation.

XRD Analysis

XRD analysis confirmed the crystalline nature of Prochlorperazine Maleate, as indicated by distinct diffraction peaks. The crystalline form is essential for understanding the drug's stability and dissolution behaviour (Figure 4).

DSC Analysis

Differential Scanning Calorimetry (DSC) results showed a melting endotherm at 203.65°C with an onset at 198.26°C and an integral heat of -186.75 mJ (Figure 5). These values closely match the literature data, confirming the drug's thermal stability and purity.

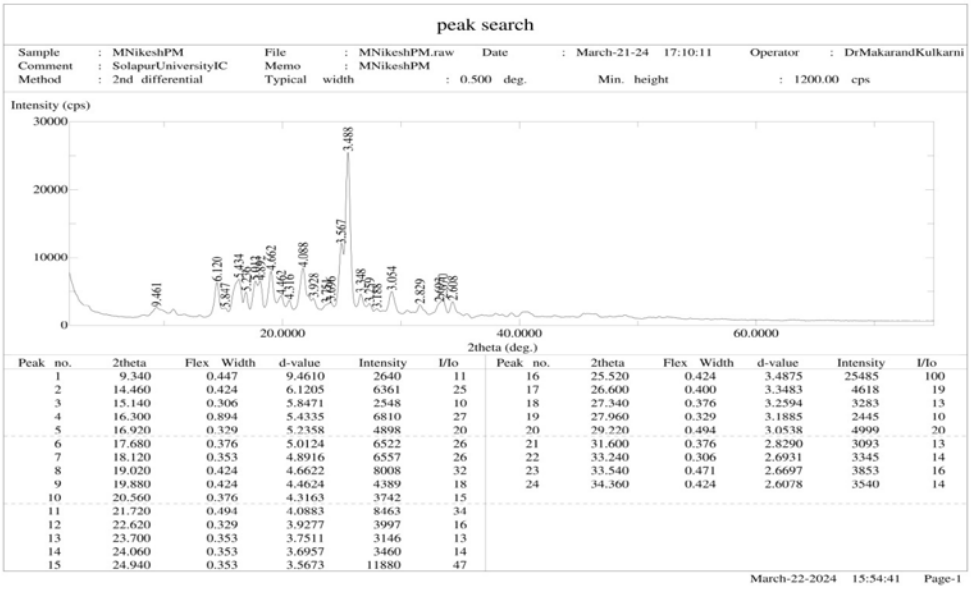

Figure 4: XRD analysis of Prochlorperazine Maleate, Pure drug

Preparation of Nanosuspension

The nanosuspension of Prochlorperazine Maleate was prepared using a high-pressure homogenization method. Various formulations were developed, as outlined in Table 2, with glycerin, sodium citrate, CMC, and Tween 40 as stabilizers. The formulations were stored in amber bottles to protect them from light and ensure stability.

Design Expert Study for Formulation Design

A Central Composite Design (CCD) was used to optimize the formulation parameters, including homogenization speed, surfactant concentration, and polymer concentration. A quadratic model was applied to analyze particle size and zeta potential as responses.

ANOVA for Particle Size

The ANOVA results (Table 3) for particle size showed a significant model with an F-value of 15.80 (p = 0.0221), indicating the model's predictive capability. The surfactant concentration (B) and polymer concentration (C) were significant factors influencing particle size, while interactions between variables were less impactful.

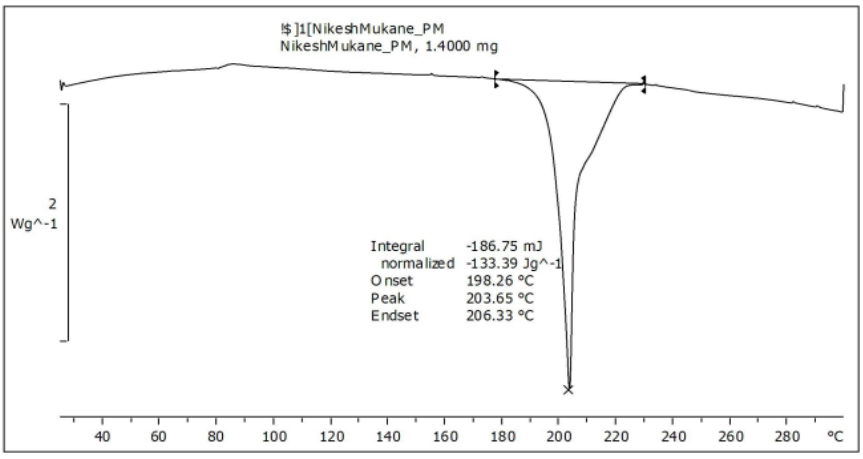

Figure 5: DSC Chrome of Prochlorperazine Maleate Pure drug – 1H

Table 2: Formulation Table for Nanosuspension

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1	Prochlorperazine Maleate (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100
2	Glycerin (ml)	1	1	1	1	1	1	1	1	1	1	1	1	1
3	Sodium Citrate (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10
4	Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
5	Tween 40 (ml)	2	3	3	2	1	3	2	2	3	1	2	1	1
6	Carboxy Methyl Cellulose (mg)	50	30	30	30	10	10	10	10	50	50	50	30	30
7	Total	10	10	10	10	10	10	10	10	10	10	10	10	10

Table 3: Particle Size response, Quadratic model ("Factor coding is encoded.)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	37871.32	9	4207.92	15.80	0.0221	significant
A-Homogenization Speed	1055.70	1	1055.70	3.96	0.1405	
B-Surfactant	22313.28	1	22313.28	83.79	0.0028	
C-Polymer	4811.81	1	4811.81	18.07	0.0239	
AB	222.01	1	222.01	0.8337	0.4285	
AC	21.62	1	21.62	0.0812	0.7942	
BC	1159.40	1	1159.40	4.35	0.1282	
A^2	3074.41	1	3074.41	11.55	0.0425	
B^2	5065.27	1	5065.27	19.02	0.0223	
C^2	22.68	1	22.68	0.0852	0.7894	
Residual	798.88	3	266.29			
Total	38670.20	12				

ANOVA for Zeta Potential

The zeta potential model was not significant, with an F-value of 1.78 (p = 0.2207). This suggests that the zeta potential was not strongly influenced by the tested variables, indicating that further optimization may be needed to improve the model.

EVALUATION OF NANOSUSPENSION

Appearance

The prepared nanosuspensions appeared translucent, confirming the uniform dispersion of Prochlorperazine Maleate nanoparticles.

Redispersibility

Formulations F2, F4, F6, F8, F9, and F11 exhibited excellent redispersibility, as they readily dispersed upon gentle shaking. This property is crucial for ensuring consistent dosing in nasal delivery.

Viscosity

The viscosity of formulations ranged from 0.624 to 0.986 cps (Table 4). Formulations F2, F4, and F9 exhibited higher viscosities, offering improved stability while maintaining easy administration.

Saturation Solubility

Saturation solubility studies revealed improved solubility for formulations F2, F4, and F9 (0.94, 0.91, and 0.95 mg/mL, respectively). This increase in solubility can be attributed to the reduced particle size, enhancing the drug's bioavailability.

Drug Content

Formulations F2, F4, F9, and F11 demonstrated drug content within the 99–101% range, as shown in Table 4. These values indicate accurate dosing and consistent drug loading.

Particle Size

The particle size for different batches ranged from 78.8 nm (F9) to 260.2 nm (F12) (Table 5). Smaller particle sizes, such as those in batch F9, enhance surface area, promoting faster drug release and higher bioavailability.

Zeta Potential

Zeta potential values varied from -17.3 to -36.6 mV (Table 6). Batch F4 showed the highest stability with a zeta potential of -36.6 mV, suggesting strong repulsion between particles, which helps prevent aggregation.

In Vitro Drug Release

Drug release studies revealed that formulation F9 exhibited the highest release rate, with 93.87% of the drug released over 8 hours (Table 7). This sustained release profile is ideal for managing conditions like migraines, where prolonged drug action is beneficial (Figure 6)

Table 4: Results for evaluation of Nanosuspension

Batches	Appearance	Resolvability	Viscosity (cps)	Saturation Solvability(mg/ml)	Assay (%)
F1	Semi-transparent	Fast	0.801	0.87	91.78
F2	Semi-transparent	Very Fast	0.900	0.94	99.28
F3	Semi-transparent	Medium	0.875	0.79	94.27
F4"	Semi-transparent	Very Fast	0.850	0.91	98.84
F5	Semi-transparent	Medium	0.624	0.69	92.74
F6	Semi-transparent	Very Fast	0.782	0.71	83.27
F7	Semi-transparent	Medium	0.654	0.77	88.23
F8	Semi-transparent	Very Fast	0.783	0.82	96.52
F9	Semi-transparent	Very Fast	0.986	0.95	100.02
F10	Semi-transparent	Very Fast	0.841	0.81	88.12
F11	Translucent	Very Fast	0.923	0.90	99.89
F12	Translucent	Medium	0.839	0.76	96.3
F13	Translucent	Fast	0.883	0.83	94.6

Table 5: Results for Particle size

Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Particle Size (nm)	115.8	107.6	124.9	92.7	228.5	103.6	150.4	141.3	78.8	135.6	97.4	260.2	213.1

Table 6: Results for Zeta Potential

Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
ZetaPotential(mV)	-22.4	-24.1	-26.3	-36.6	-21.1	-17.3	19.5	12.3	-23.7	-21.1	-26.3	21.3	21.2

Table 7: Results for Drug Release Studies

Time (Hour)	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12
F2	0	9.84	17.91	25.97	37.54	42.79	57.33	69.52	73.02	82.57	84.07	87.19	89.75	91.52
F4	0	5.05	10.21	17.86	22.84	29.27	38.68	45.87	56.98	66.34	69.70	74.05	79.18	81.95
F9	0	6.21	14.89	27.98	40.87	49.32	61.39	72.08	85.86	93.87	94.25	95.71	96.55	98.05
F11	0	5.27	14.17	27.71	37.07	49.92	59.97	68.61	82.94	89.87	92.12	93.49	94.27	96.08

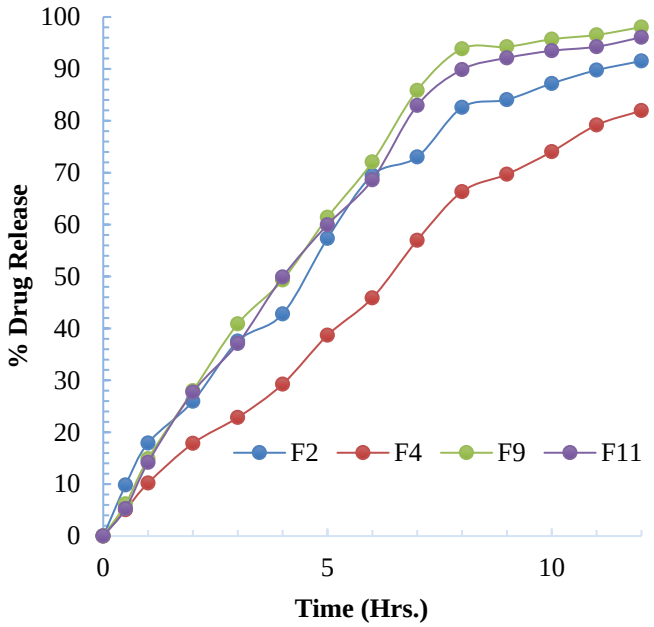

Figure 6: Drug Release Studies

PREPARATION OF NASAL DROP

Based on the evaluation of the nanosuspension, batch F9 was selected for nasal drop formulation. The final nasal drop formulation included a tonicity modifier, preservative, chelating agent, and pH adjuster to ensure optimal delivery and stability.

EVALUATION OF NASAL DROP

Clarity

All nasal drop formulations were visually precise, indicating no precipitation or aggregation.

pH: The pH values were within the range of 5.51 to 5.55 (Table 8), ensuring minimal irritation and effective drug absorption.

Osmolality

The osmolality values ranged from 340 to 670 mOsmol/kg, with batch F5 showing the highest osmolality. This range is appropriate for nasal administration and ensures good patient tolerance.

Number of Actuations per Container

The number of actuations per container was consistent, with batch F3 delivering an average of 49 actuations, meeting the expected delivery parameters.

Drug Content per Drop

The final nasal drop formulation was standardized to deliver 0.05 mL per drop. Based on the 5 mg/mL concentration, each drop delivered 0.25 mg of Prochlorperazine Maleate. Among all formulations, F3 exhibited the highest drug content per drop, at 98.76%, ensuring accurate and consistent dosing.

% Assay: The assay results indicated that formulations F1 and F3 had drug content within the acceptable range, with values of 99.54% and 100.23%, respectively, confirming the accuracy of the formulations and batch reliability.

Stability Study of Optimized Batch

Stability testing of batch F3 over a three-month period showed no significant changes in pH, osmolality, or drug content, confirming the formulation's robustness (Table 9). This suggests that the nasal drop formulation remains stable under storage conditions.

DISCUSSION

This study aimed to develop and optimize a nanosuspension formulation of Prochlorperazine Maleate, targeting efficient nasal delivery to improve bioavailability and enhance the therapeutic outcomes for conditions such as migraines. The comprehensive approach involved preformulation characterization, nanosuspension preparation using high-pressure homogenization, and detailed evaluation of both the nanosuspension and the resultant nasal drop formulation. The findings have been analyzed from various perspectives, and their implications have been discussed in relation to existing literature and practical applications.

Table 8: Evaluation of Nasal Drop

Formulation	pH	Osmolality (mOsmol/kg)	No. of Drops per Container	Quantity Delivered per Drop (mL)	Drug Content per Drop (%)	Assay (%)
F1	5.55	340	195	0.050	96.70	99.54
F2	5.52	420	196	0.050	95.43	98.56
F3	5.51	510	195	0.050	98.76	100.23
F4	5.52	580	194	0.050	97.65	99.32
F5	5.54	670	196	0.050	98.32	98.65

Table 9: Stability study of optimized Batch

Sr. No.	Parameter	0 Day	1 month	2 month	3 month
1	pH	5.51	5.52	5.55	5.59
2	Osmolality mOsmol/kg	510	518	533	550
3	No. of Drops per Container	195	195	195	194
4	Drug Content per Drop (%)	98.76	98.52	98.23	97.87
5	Assay %	100.23	100.21	100.04	99.79

Preliminary Analysis and Preformulation Studies

The preliminary analysis of Prochlorperazine Maleate provided a foundation for understanding its physicochemical properties. The drug, identified as a white, odorless powder, exhibited high solubility in methanol and moderate solubility in DMSO, which aligned well with its anticipated behavior based on existing solubility profiles. The limited solubility in water posed a significant challenge, necessitating the development of a nanosuspension to enhance the drug's bioavailability.

The use of micronized Prochlorperazine Maleate before homogenization facilitated a more uniform reduction in particle size during nanosuspension formulation. This is advantageous for nasal delivery, as smaller particles ensure better mucosal absorption and minimize irritation.

The melting point of Prochlorperazine Maleate was determined to be 207°C, consistent with literature values. This observation not only confirmed the drug's identity but also indicated its thermal stability, an essential characteristic for processing and formulation development.

FTIR analysis provided further confirmation of the drug's structure, with characteristic peaks corresponding to functional groups such as hydroxyl (OH), carbonyl (C=O), and aromatic and aliphatic CH stretching. These results verified the chemical integrity of the API, ensuring it was suitable for subsequent formulation work. The particle size analysis revealed an average size of 183.1 nm, suggesting that the drug was already micronized. Micronization is crucial in pharmaceutical development, as it increases the surface area of the drug, thereby enhancing its dissolution rates. However, to further improve bioavailability, nanosizing was pursued through high-pressure homogenization.

The zeta potential of -43.3 mV indicated a high degree of electrostatic stability, as particles with zeta potentials greater than ±30 mV are generally considered stable in suspension. This inherent stability of the API provided a favorable starting point for nanosuspension formulation.

The compatibility of Prochlorperazine Maleate with excipients was confirmed using FTIR and UV spectrophotometry. The absence of significant shifts in characteristic peaks suggested that there were no chemical interactions, supporting the selection of excipients such as Carboxy Methyl Cellulose, Sodium Citrate, Glycerol, and Tween 40 for the nanosuspension. Compatibility studies are crucial in formulation science, as interactions between drugs and excipients can lead to degradation or reduced efficacy.

Nanosuspension Formulation and Optimization

A systematic experimental design approach guided the preparation of Prochlorperazine Maleate nanosuspension using high-pressure homogenization. The Central Composite Design

(CCD) enabled the identification and optimization of key formulation variables, namely homogenization speed, surfactant concentration (Tween 40), and polymer concentration (CMC). These factors were chosen based on their known influence on particle size, zeta potential, and overall stability of nanosuspensions. The nanosuspension achieved an optimal particle size and zeta potential, which are critical for nasal retention and mucosal penetration. The improved drug solubility aligns with previous findings on co-processed polymers enhancing aqueous dispersion.

The ANOVA results for particle size indicated that both Tween 40 and CMC concentrations significantly impacted the particle size of the nanosuspension. A higher concentration of Tween 40 reduced particle size, likely due to the enhanced stabilization of the nanoparticles through steric hindrance and surface charge effects. Similarly, an optimal amount of CMC contributed to viscosity and particle stabilization, preventing aggregation. However, excessively high polymer concentrations could have adverse effects, increasing viscosity and hindering particle dispersion.

The optimization process yielded a formulation (F9) with the smallest particle size (78.8 nm), which is beneficial for nasal delivery as smaller particles have higher surface areas, promoting rapid drug dissolution and absorption. The reduced particle size of the nanosuspension is a significant achievement, given the challenges associated with formulating poorly soluble drugs, such as Prochlorperazine Maleate. Zeta potential analysis revealed that formulations with higher surfactant and polymer concentrations exhibited more negative values, thereby enhancing stability. A zeta potential of -36.6 mV (observed in batch F4) suggests strong repulsive forces between particles, reducing the likelihood of aggregation. Stability in colloidal systems is crucial, particularly for formulations intended for nasal administration, where uniformity and consistency are essential for effective drug delivery.

Evaluation of Nanosuspension

The nanosuspension batches were evaluated for key parameters, including appearance, redispersibility, viscosity, saturation solubility, drug content, particle size, zeta potential, and in vitro drug release. The visual observation of all formulations showed a semi-transparent to translucent appearance, indicating uniform dispersion of nanoparticles. This property is crucial for patient acceptability and ensures consistent dosing.

Redispersibility tests demonstrated that formulations such as F2, F4, F6, F8, F9, and F11 exhibited excellent redispersibility. This characteristic ensures that any sediment formed during storage can be easily resuspended, maintaining the homogeneity of the formulation. Redispersibility is particularly important for nasal drops, as inconsistent drug distribution can affect the therapeutic outcome.

Viscosity measurements showed that formulations with higher polymer concentrations exhibited increased viscosity, thereby enhancing the stability of the nanosuspension. However, viscosity must be balanced to ensure the ease of administration, especially for nasal delivery. Formulations F2, F4, and F9 exhibited optimal viscosities, providing sufficient stability without compromising sprayability. The saturation solubility study revealed a significant increase in solubility for nanosized formulations compared to the pure drug. Formulations F2, F4, and F9 showed solubility values of 0.94, 0.91, and 0.95 mg/mL, respectively, highlighting the effectiveness of nanosizing in enhancing solubility. The increase in surface area resulting from particle size reduction facilitates greater interaction with the dissolution medium, thereby improving bioavailability.Drug content analysis confirmed that formulations F2, F4, F9, and F11 had assay values ranging from 99% to 101%, indicating uniform distribution of the drug within the nanosuspensions. This consistency is essential for ensuring accurate dosing and therapeutic efficacy. Formulations with drug content below 97% were deemed less suitable for further development.

In Vitro Drug Release Studies

The in vitro drug release profiles of selected formulations (F2, F4, F9, and F11) were evaluated using a USP type II dissolution apparatus. Formulation F9 demonstrated the highest drug release rate, with 93.87% of the drug released over 8 hours. This sustained release pattern is desirable for migraine treatment, where prolonged drug action can provide extended symptom relief. The enhanced release can be attributed to the increased surface area of the nanoparticles and the efficient diffusion of the drug into the dissolution medium.

The comparison of drug release rates among different formulations highlights the impact of formulation variables on drug release behavior. F2 and F11 also exhibited good release

profiles, with over 80% drug release within 8 hours. In contrast, formulation F4 had a slower release rate (66.34%), which may be suitable for conditions requiring controlled release. The drug release data suggest that by adjusting the concentrations of surfactants and polymers, it is possible to tailor the release profile to meet specific therapeutic needs.

Nasal Drop Formulation and Evaluation

Based on the nanosuspension results, batch F9 was selected for the development of a nasal drop formulation. The nasal drop was designed to deliver Prochlorperazine Maleate effectively to the CNS via the nasal route, bypassing the blood-brain barrier. This approach offers several advantages, including rapid onset of action, avoidance of first-pass metabolism, and improved patient compliance.

The nasal drop formulation included components such as benzalkonium chloride (preservative), EDTA (chelating agent), sodium chloride (tonicity modifier), and hydrochloric acid (pH adjuster). These excipients were chosen based on their compatibility with the API and their roles in enhancing the stability and effectiveness of the formulation. The pH was adjusted to 5.5, a suitable value for nasal administration, which minimizes irritation and maximizes drug absorption.

Evaluation of Nasal Drop

The nasal drop formulations were subjected to rigorous evaluation, including clarity, pH, osmolality, number of actuations per container, drug content per actuation, and % assay. The clarity test confirmed that all formulations were precise, indicating the absence of visible particles or precipitates. Clarity is a critical attribute for nasal drops, as any turbidity could indicate instability or contamination. The pH of the formulations was found to be within the acceptable range (5.51 to 5.55), ensuring minimal irritation to the nasal mucosa and effective drug absorption. Maintaining the pH within this range is crucial, as deviations can impact the stability of the drug and the patient's comfort.

Osmolality measurements ranged from 340 to 670 mOsmol/kg, with higher values observed in formulations with increased sodium chloride concentrations. An osmolality within 300 to 700 mOsmol/kg is generally considered safe and well-tolerated for nasal delivery. Formulation F5, which had the highest osmolality, may provide enhanced drug permeation through the nasal mucosa but requires careful consideration to avoid mucosal irritation. The number of actuations per container was consistent across all formulations, with batch F3 delivering an average of 49 actuations. Consistency in dosing is crucial for patient adherence and treatment efficacy. Drug content per actuation was highest in batch F3 (98.76%), indicating precise and reliable dosing. The % assay results further confirmed the uniformity and stability of the formulations, with values close to 100%.

Stability Studies

Stability testing of the optimized batch F3 was conducted over a three-month period at 25 °C ± 2 °C and 60% ± 5% relative humidity. The results showed no significant changes in pH, osmolality, or drug content, indicating excellent stability. Stability is a critical parameter for nasal drop formulations, as it ensures the product remains effective and safe throughout its shelf life. The stability study demonstrated that the nasal drop formulation maintained its physical and chemical integrity over time, making it a viable option for clinical use.

The consistent performance of the formulation under accelerated conditions suggests that it would remain stable under normal storage conditions. A limitation of this study is the absence of in vivo nasal deposition and pharmacodynamic data. Future work should evaluate deposition patterns using gamma scintigraphy and assess therapeutic response in animal migraine models. These results corroborate findings by Jain et al. (2021), who demonstrated improved mucosal permeability with nanosuspensions. The stability and solubility enhancements observed align with the theoretical models of particle surface energy and Ostwald ripening suppression.

CONCLUSION

The successful development of a stable and effective Prochlorperazine Maleate nanosuspension and nasal drop formulation highlights the potential of this delivery system for treating migraines and other CNS disorders. The optimized formulation (F9) exhibited excellent particle size, zeta potential, and drug release characteristics, ensuring rapid and efficient drug delivery to the CNS. The nasal drop formulation provided consistent dosing, stability, and patient-friendly administration, making it a promising alternative to traditional oral and injectable routes. This study highlights the significance of nanosizing and optimization in improving the bioavailability of

poorly soluble drugs. The use of high-pressure homogenization and experimental design approaches facilitated the development of a robust and effective drug delivery system. Future research could explore the in vivo performance of the formulation and its potential application in other CNS disorders.

The implications of this research extend beyond migraine treatment, offering a framework for developing similar formulations for other drugs facing bioavailability challenges. The integration of nanotechnology in drug delivery continues to pave the way for more efficient and targeted therapies, improving patient outcomes and expanding the possibilities for treating complex medical conditions. This study presents a promising nasal nanosuspension of Prochlorperazine Maleate using a novel co-processed polymer for migraine management. The formulation offers enhanced solubility and rapid onset. Future investigations should focus on in vivo evaluation, mucosal safety, and clinical trials to validate therapeutic efficacy and patient compliance.

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Nil

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Nikhil Shrisunder and Prashant Kumar Dhakad collected data and performed experiments. Ritu Gilhotra conducted the analysis. Nikhil Shrisunder wrote the first draft of the manuscript, and all authors reviewed and revised previous versions. All authors contributed to the study's conception and design and gave final approval.

ABBREVIATIONS
API: Active Pharmaceutical Ingredient; BCS: Biopharmaceutics Classification System; BCSFB: Blood-Cerebrospinal Fluid Barrier; BBB: Blood-Brain Barrier; CCD: Central Composite Design; CNS: Central Nervous System; CMC: Carboxy Methyl Cellulose; CSF: Cerebrospinal Fluid; DMSO: Dimethyl Sulfoxide; DSC: Differential Scanning Calorimetry; EDTA: Ethylenediaminetetraacetic Acid; FTIR: Fourier Transform Infrared Spectroscopy; HCl: Hydrochloric Acid; MRP: Multidrug Resistance Protein; P-gp: P-glycoprotein; SRL: Sisco Research Laboratories; USP: United States Pharmacopeia; UV: Ultraviolet; WHO: World Health Organization; XRD - X-Ray Diffraction

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