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FORMULATION AND EVALUATION OF TRAZODONE HCL LOADED THERMO-REVERSIBLE *IN-SITU* INTRANASAL GEL

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ABSTRACT: This study aimed to design and evaluate a thermoreversible, mucoadhesive intranasal gel formulation of Trazodone HCl for enhanced drug delivery to the brain. Pre-formulation processes involved characterization of the drug using UV spectroscopy, FTIR, and DSC techniques to confirm drug purity and compatibility with excipients. The nasal gel was formulated using Poloxamer 407 (19%) and Carbopol 934P (0.1% - 0.5%) through the cold method. The formulated gels were evaluated for pH, clarity, viscosity, mucoadhesive strength, *in-vitro* drug release, and ex vivo permeation across goat nasal mucosa. Gelation temperature was optimized to align with physiological nasal temperatures (32–34°C), and results demonstrated effective sol-to-gel transitions. Drug release studies revealed over 85% release from optimized formulation (A4) within 8 hours. *Ex-vivo* permeation studies confirmed significant drug absorption through the nasal membrane, with A4 exhibiting 78.45% cumulative drug release. Stability studies validated the formulations' reliability, and no incompatibilities were observed between drug and excipients. This intranasal gel formulation represents a promising, non-invasive approach to improve the bioavailability and therapeutic efficacy of Trazodone HCl for treating depression.

INTRODUCTION: Depression is a prevalent mental disorder affecting over 280 million people globally, characterized by persistent sadness, hopelessness, fatigue, and loss of interest. As a leading cause of disability, it significantly impacts productivity and quality of life. Conventional oral treatments for depression face challenges like low bioavailability (65%) due to extensive first-pass metabolism [1]. Trazodone HCl, a selective serotonin reuptake inhibitor (SSRI), is commonly used but suffers from limited brain targeting.

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To overcome these challenges, intranasal drug delivery systems offer a promising approach by bypassing the blood-brain barrier (BBB) and hepatic metabolism. Thermoreversible in situ gels, formulated using Poloxamer 407 and Carbopol 934P, exhibit sol-to-gel transition at physiological temperatures, enhancing nasal residence time and improving drug absorption. This study focuses on the formulation and evaluation of a Trazodone HCl-loaded thermoreversible intranasal gel to improve drug delivery to the brain [2].

MATERIALS AND METHODS: Trazodone HCl, Carbopol 934P, and Poloxamer 407 were sourced from Yarrow Chem. Products in Mumbai, while all other solvents and chemicals were obtained from reliable and authenticated suppliers. This ensured the quality and consistency of

materials used in the formulation process, adhering to established standards for pharmaceutical research and development.

Gelation Temperature Determination [3, 4]: A visual inspection method was adopted to determine the gelation temperature. Poloxamer 407 solutions 15-20% w/v were prepared and measured. About 10 mL of each solution was kept on a hot plate magnetic stirrer, heating at 32–34º C. Gelation or transition temperature was noticed at 32-34º C, where rotation of the magnetic bead stopped due to gel formation. Different concentrations, i.e., 0.1–0.5% w/v of carbopol 934P in poloxamer 407 solution, at which gelation took place were used for further study.

Formulation of Trazodone HCl *In-situ* Intranasal Gel [5, 6]: *In-situ* nasal gels were prepared by cold technique. Various batches of A1 to A5 were formulated as presented in **Table 1.** The Carbopol 934P was dissolved completely in cold water to get solutions ranging from 0.1 to 0.5 % w/v of the Carbopol 934P.

Poloxamer 407 was added into above solution (19 % w/v). These solutions placed in cool condition (4-8 °C) overnight so that Poloxamer 407 gets completely dissolved. Trazodone HCL dissolved completely in those solutions (1.25%). This formulated solution store Formulated gels where then finally stored at 4 °C for further evaluation.

TABLE 1: FORMULATION OF *IN-SITU* INTRANASAL GEL OFTRAZODONE HCL

Formulation Batch	Carbopol 934P % w/v	Poloxamer 407 % w/v	Trazodone HCL % w/v
A1	0.1	19	1.25
A2	0.2	19	1.25
A3	0.3	19	1.25
A4	0.4	19	1.25
A5	0.5	19	1.25

Evaluation of *In-situ* Gels:

Physico-chemical properties of Trazodone HCl *In-situ* Gel: The formulated gels were evaluated for their physicochemical properties viz-pH, clarity and drug content.

pH [7]: The pH of each formulation was examined by using digital pH meter (EQ-614A, Equip-Tronics). The pH meter was first calibrated using buffer solutions of pH 4 and pH 7. Then gels were taken in a beaker and their pH was measured.

Clarity [7]: The appearance of the gels was examined for clarity. The clarity of various formulations was evaluated by visual inspection under black and white backgrounds.

Drug Content Determination [8, 9]: In this study, each formulation (1 ml) was taken in a 100-ml volumetric flask diluted with distilled water up to the mark. After suitable dilutions the amount of drug was measured in the formulation by using UV spectroscopy at 246 nm.

Rheological Study [10]: The viscosity of the developed formulations was measured using a Brookfield programmable rheometer (Brookfield DV-I Prime, Brookfield Engineering Laboratories, Inc.). Each gel sample was placed in a 100 mL beaker, and viscosity was determined with spindle no. 64 at a constant rotational speed of 50 RPM, maintained at a temperature of 10 ± 1°C. The temperature was gradually increased in increments of 10°C during testing, with viscosity readings taken immediately after reaching each new temperature. All measurements were conducted in triplicate to ensure reliability and precision of the results.

Determination of Mucoadhesive Strength [11, 12]: The mucoadhesive potential of each formulation was evaluated by measuring the force required to detach it from sheep nasal mucosal tissue. Nasal mucosa sections were obtained from a local slaughterhouse, separated from underlying bone cartilage, and cut into small pieces. Two tissue portions were affixed to separate glass slides using thread. One slide was secured beneath a pan balance using adhesive tape, positioned so the tissue faced downwards. The other slide was fixed on a wooden board of the balance with the tissue positioned just below the upper tissue.

A 100 mg sample of gel was placed between the two mucosal tissues and held in contact for 2 minutes. Gradual addition of dummy granules to the other pan caused separation of the tissues and movement of the slides apart. Fresh nasal mucosa was used for each measurement. The mucoadhesive strength of formulations A1 to A5 was quantified as detachment stress in dyne/cm², determined by the minimal weight needed to separate the mucosal tissues.

$$\text{Mucoadhesive strength} = (m \times g) / A \times 100$$

Where, m = weight of granules required to separate the tissues, g = acceleration due to gravity (980 cm/s2), A = area of mucosa exposed.

The nasal mucosa was changed for each measurement.

***In-vitro* Drug Release Study [13, 14]:** The drug release from the gel was assessed using a locally fabricated Franz diffusion cell equipped with a dialysis membrane (molecular weight cutoff: 12,000– 14,000 Daltons). The receptor chamber contained 37 mL of saline phosphate buffer (pH 7.4), while the donor compartment held gel equivalent to 2.5 mg of the drug. The dialysis membrane, pre-soaked in the receptor medium for 2 hours, separated the two compartments. The temperature of the receptor medium was maintained at 32 ± 1°C throughout the study duration. At specific time intervals up to 12 hours, 0.5 mL samples were withdrawn from the receptor compartment and replaced with fresh buffer. These samples were then appropriately diluted and analyzed spectrophotometrically at 246 nm. The amount of drug released was quantified using a calibration curve established beforehand.

***Ex-vivo* Drug Permiation Evaluation [15, 16]:** Nasal cavity of goat was obtained from local slaughter house immediately after its sacrifice.

It was safely transported to laboratory by keeping it in saline phosphate buffer (pH 7.4) Nasal septum was separated from underlying bone without damage. Tissue samples were fixed on Franz diffusion cells having effective permeation area of 0.785 cm^2. After 30 min of incubation time the thermoreversible gel formulations were placed in the donor compartment. The temperature of the chambers was maintained at 34 °C. Saline phosphate buffer pH 7.4 was used as receptor medium. The sampling was done at predetermine time intervals for 8 hr and amount of drug permeated was analysed by UV spectrophotometer at 246 nm.

Stability Study: The stability of the gels was assessed by placing samples in glass vials and sealing them with aluminium foil to ensure airtight conditions. These samples were stored under controlled conditions at 5°C ± 3°C for a duration of one month. At the end of this period, the samples were analyzed to determine drug content, gelation temperature, and other physical characteristics. This approach aimed to ascertain the stability and reliability of the gel formulations under simulated storage conditions, providing critical data for assessing their potential for pharmaceutical applications.

RESULTS AND DISCUSSION:

Gelation Temperature Determination: Determining the phase transition temperature is critical in formulating thermoreversible gels designed for intranasal delivery. These gels need to transition from a liquid state at room temperature to a gel state within a specific temperature range suitable for the nasal administration, typically between 25°C and 34°C. If the gelation temperature is too low, there's a risk of premature gelling during handling and storage. On the other hand, if the temperature is too high, the gel may not form adequately in the nasal cavity, potentially affecting drug delivery efficiency. Poloxamer 407, a thermoreversible polymer known for its ability to form micelles, plays a crucial role in this process.

Studies have shown that a minimum concentration of 19% w/v Poloxamer 407 is required to achieve gelation within the optimal temperature range of 32-34°C. Further adjustments in the Poloxamer concentration, such as increasing from 18% to 20%, can significantly impact the gelation temperature, lowering it from 34°C to 26°C. Additionally, Carbopol 934P, which enhances mucoadhesion, also contributes to lowering the gelation temperature when present at concentrations above 0.3% w/v. These insights underscore the importance of carefully optimizing polymer concentrations to achieve the desired

phase transition temperature, ensuring effective gel formation for intranasal drug delivery while maintaining stability under various storage condition.

TABLE 2: EFFECT OF CARBOPOL 934P CONCENTRATIONS ON PHASE TRANSITION TEMPERATURE

Sr. no.	Sample (w/v) (% Poloxamer 407 + % Carbopol 934P) (%)	Gelling temperature (°C)
1	19 + 0.1	34-35
2	19 + 0.2	33-34
3	19 + 0.3	32-33
4	19 + 0.4	31-32
5	19 + 0.5	28-29

Drug Content Determination: The drug content of the gels was determined spectrophotometrically and found to be between 96.30 and 98.20 %. of the initially added drug quantity, which is satisfactory, i.e. 1.25 % w/v in all formulations.

Viscosity Determination: The viscosity of the prepared formulations was checked when these are in sol state. The viscosity was found to be increased with increase in Carbopol 934P concentration as shown in **Fig. 1.**

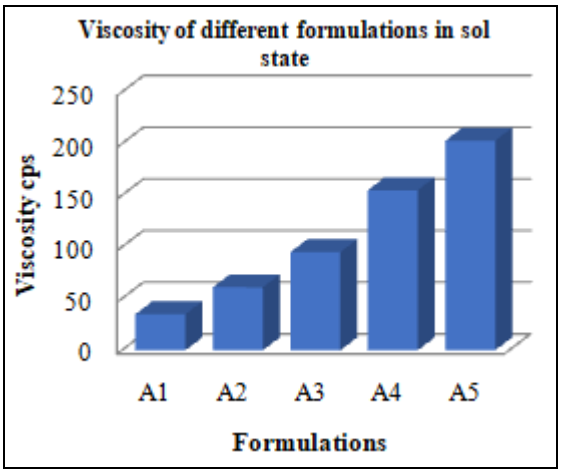

FIG. 1: VISCOSITY OF FORMULATION A1 TO A5 IN SOL STATE

Mucoadhesive Strength Determination: Mucoadhesive strength was evaluated through detachment stress, measuring the force required to separate mucous membranes. The study revealed that varying concentrations of Carbopol 934P exerted a notable influence on the mucoadhesive properties within the formulations. Increasing the concentration of this mucoadhesive polymer led to a decrease in gelation temperature and a proportional increase in mucoadhesive strength. Up to a concentration of 0.4% w/v Carbopol 934P, mucoadhesive strength remained below 7,000 dynes/cm². Beyond this threshold, mucoadhesive strength escalated sharply, surpassing 9,000 dynes/cm² with further increases in Carbopol 934P concentration (refer to **Fig. 2**). Carbopol 934P, characterized by its cross-linked polyacrylate structure rich in carboxylic groups, forms hydrogen bonds with sugar residues on mucous membranes, enhancing adhesion. This study underscores the critical role of Carbopol 934P concentration in influencing mucoadhesive properties, particularly evident in formulations A2, A3, A4, and A5, which demonstrated sufficient mucoadhesive strength as per the study's findings.

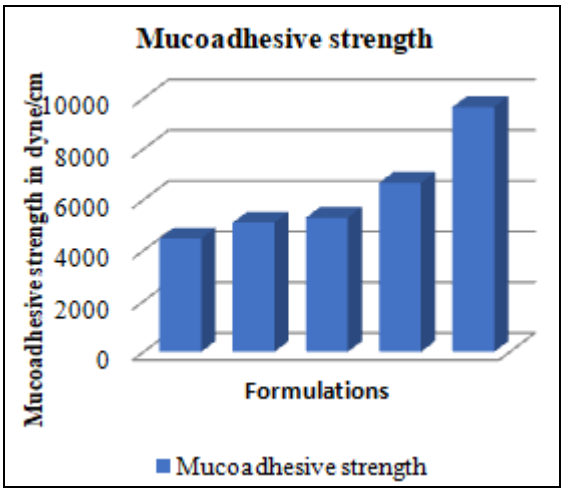

FIG. 2: MUCOADHESIVE STRENGTH OF FORMULATION A1 TO A5

TABLE 3: MUCOADHESIVE STRENGTH FORMULATION A1 TO A5

Sr. no.	Formulations	Mucoadhesive strength
1	A1	4468.8
2	A2	5096.3
3	A3	5292.7
4	A4	6664.6
5	A5	9653.3

***In-vitro* Drug Release Study:** The drug release characteristics of the thermoreversible intranasal gel were evaluated using a Franz diffusion cell, with the temperature maintained between 32–34°C for a duration of 8 hours.

The findings revealed that all formulations achieved a drug release of over 65% by the end of the study, as shown in **Fig. 3.** Each formulation displayed a unique inflection point in its release profile, indicating the formation of a gel within the donor compartment. This gel likely captured a portion of the drug within the polymer matrix, which contributed to a slower release rate due to enhanced cross-linking in the gel structure. Additionally, Poloxamer contributed to this mechanism by facilitating micelle formation and enhancing the structural integrity of the gel. Among the formulations tested, A1 and A4 batches demonstrated the highest release rates, both surpassing 85%. Consequently, formulation A4 was selected for further *ex-vivo* studies, showcasing its promising potential for intranasal drug.

TABLE 4: *IN-VITRO* % DRUG RELEASE OF FORMULATION A1 TO A5 BATCHES

Sr. no.	Time in	% Drugrelease				
	Minute	A1	A2	A3	A4	A5
1	0	0	0	0	0	0
2	120	16.2	25.3	20.15	23.6	12.3
3	240	40.6	49.55	41.39	46	27.2
4	360	78.7	52.8	55.2	75.4	54.9
5	480	82.1	74	66.67	85.1	60.4

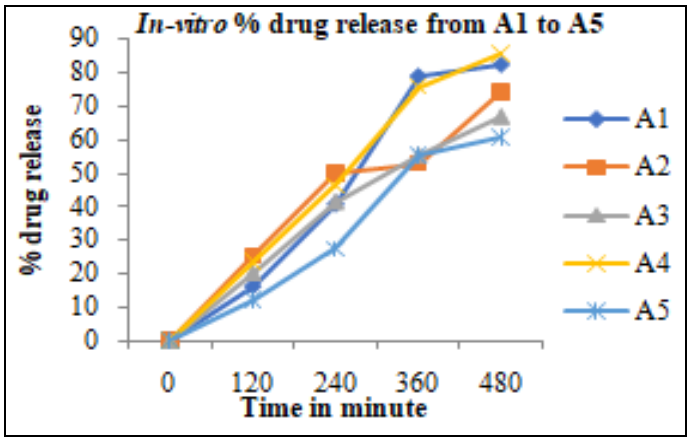

FIG. 3: *IN-VITRO* % DRUG RELEASE OF FORMULATION A1 TO A5 BATCHES

***Ex-vivo* Drug Permeation Evaluation:** The nasal cavity of a goat was obtained from a local slaughterhouse immediately after sacrifice and transported to the laboratory in a saline phosphate buffer (pH 7.4). The nasal septum was carefully separated from the underlying bone to avoid any damage. Tissue samples were mounted onto Franz diffusion cells with a permeation area of 0.785 cm². After a 30-minute incubation period, the thermoreversible gel formulations were applied to the donor compartment, with the chamber temperature maintained at 34°C. A saline phosphate buffer with a pH of 7.4 was used as the receptor medium. Sampling was conducted at set time intervals over 8 hours, and the drug permeated was analyzed using a UV spectrophotometer at 246 nm.

TABLE 5: *EX-VIVO* % DRUG PERMEATION OF A4

Sr. no.	Time in minute	Absorbance	Conc./ml	Conc./0.5ml	CDR	%CDR
1	0	0	0	0	0	0
2	60	0.07	11.29032	5.645161	0.225806	9.032258
3	120	0.126	20.32258	10.16129	0.406452	16.25806
4	180	0.235	37.90323	18.95161	0.758065	30.32258
5	240	0.385	62.09677	31.04839	1.241935	49.67742
6	300	0.467	75.32258	37.66129	1.506452	60.25806
7	360	0.543	87.58065	43.79032	1.751613	70.06452
8	420	0.584	94.19355	47.09677	1.883871	75.35484
9	480	0.608	98.06452	49.03226	1.96129	78.45161

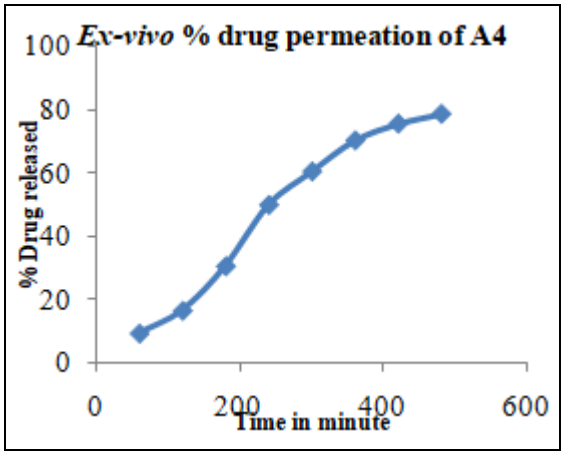

FIG. 4: *EX-VIVO* % DRUG PERMEATION OF FORMULATION A4

Stability Studies: The gels stability was tested after one month by measuring drug content, gelation temperature, and clarity. Gelation temperatures remained consistent for all samples, and drug content ranged from 95% to 98.5%. Most formulations were clear, except for A5, which was opaque. The opacity in A5 might be due to its higher level of Carbopol 934PP, which could have affected the gel structure and density.

CONCLUSION: Trazodone HCL, classified as an SSRI, is used to treat depression, anxiety, and other mood disorders. This study successfully formulated and evaluated a thermoreversible, mucoadhesive *in-situ* intranasal gel of Trazodone HCl. The gel's ability to transition to a liquid state upon contact with nasal mucosa enhances ease of administration and extends residence time within the nasal cavity. Utilizing a 0.4% w/v concentration of Carbopol 934P provides optimal mucoadhesive strength, improving drug permeation rates. This research concludes that the developed gel formulation represents a promising approach for safely and effectively delivering Trazodone HCL to treat depression.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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