INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Research Article

# Formulation and Evaluation of Mucoadhesive Intranasal Midodrine-Loaded Nanoemulsion for the Management of Hypotension

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ARTICLE INFO

Published: 27 Nov 2026
Keywords:
Midodrine hydrochloride, intranasal delivery, nanoemulsion, thiolated chitosan, mucoadhesion, orthostatic hypotension
DOI:
10.5281/zenodo.24583429

## ABSTRACT

Background: Midodrine hydrochloride is an orally administered prodrug used in the management of symptomatic orthostatic hypotension. Intranasal administration is a potential alternative route for systemic delivery; however, mucociliary clearance can limit nasal residence time. Mucoadhesive nanoemulsions may improve formulation contact with the nasal mucosa and modulate drug release. Objective: To formulate and evaluate thiolated-chitosan-containing mucoadhesive nanoemulsions of midodrine hydrochloride and identify a formulation with a suitable balance of physicochemical and mucoadhesive properties. Methods: Six oil-in-water nanoemulsion formulations containing midodrine hydrochloride (1% w/v), oleic acid (5% w/v), Tween 80 (20% w/v) and PEG 400 (10% w/v) were prepared with thiolated chitosan concentrations ranging from 0.1 to 0.6% w/v. Preformulation characterization, FTIR compatibility assessment, pH, viscosity, drug content, in-vitro release, mucoadhesive strength and surface morphology were evaluated. Results: The drug showed a melting point of 201 °C and a linear UV calibration response over 10–90 µg/mL ($R^2$ = 0.9996). Increasing thiolated chitosan concentration was associated with a decrease in pH (5.82–5.57), an increase in viscosity (18.42–41.38 cP) and an increase in mucoadhesive strength (0.184–0.451 N). Drug content ranged from 93.10 to 98.60%. Formulation F5, containing 0.5% w/v thiolated chitosan, showed the highest drug content (98.60 ± 0.60%), pH 5.65, viscosity 35.72 ± 0.55 cP, mucoadhesive strength 0.426 ± 0.019 N and cumulative release of 94.28 ± 1.18% at 12 h. Conclusion: F5 provided the most balanced profile among the formulations evaluated.

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**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Further droplet-size analysis, ex-vivo permeation, nasal safety, stability and in-vivo pharmacodynamic studies are required before efficacy or rapid-onset performance can be established.

## INTRODUCTION

Orthostatic hypotension is characterized by a sustained reduction in blood pressure following the assumption of an upright posture. It may present with dizziness, weakness, visual disturbance, syncope and falls, and can substantially impair daily functioning. The condition may arise from autonomic dysfunction, volume depletion, medication effects or other underlying disorders. Consensus criteria and clinical assessment are important for distinguishing orthostatic hypotension from other causes of transient symptoms [1].

Midodrine hydrochloride is a prodrug that is converted to desglymidodrine, an active metabolite that stimulates peripheral $\alpha_1$-adrenergic receptors. The resulting vasoconstriction increases peripheral vascular resistance and supports blood pressure during standing.

Clinical studies have demonstrated pressor activity in patients with neurogenic orthostatic hypotension [2,3]. Oral administration remains the established route; however, systemic exposure depends on gastrointestinal absorption and metabolic conversion. Supine hypertension is a clinically relevant risk and requires appropriate dose timing, patient counselling and monitoring.

Intranasal administration has attracted interest as a route for systemic delivery because the nasal cavity is highly vascularized and provides a relatively accessible absorptive surface. Nasal delivery can avoid gastrointestinal degradation and first-pass hepatic metabolism for suitable molecules. Nevertheless, the nasal route presents formulation challenges, including limited administration volume, enzymatic activity, variable mucosal conditions and mucociliary clearance [4,5].

Mucociliary clearance is a protective physiological process that transports deposited material toward the nasopharynx. Although essential for airway defence, it can remove a conventional nasal formulation before sufficient drug absorption occurs. Increasing the residence time of a formulation through mucoadhesion is therefore a rational formulation strategy. The design must balance adhesion with tolerability, spreadability, viscosity and the ability to deliver a reproducible dose.

The present work investigates a mucoadhesive nanoemulsion containing midodrine hydrochloride and thiolated chitosan. The formulation concept combines a dispersed lipid phase with a hydrophilic continuous phase and a polymer intended to interact with mucin. The work is an in-vitro formulation study and does not establish clinical effectiveness or a faster onset of action.

## 2. SCIENTIFIC RATIONALE

### 2.1 Nasal route as a systemic delivery pathway

The nasal cavity offers a non-invasive route for systemic drug administration. Its epithelial surface is supplied by an extensive vascular network, and the relatively thin epithelial barrier can permit absorption of appropriately designed molecules. The route may be useful when oral administration is unsuitable or when a non-invasive alternative is desirable. However, absorption is influenced by drug physicochemical properties, formulation pH, viscosity, dose volume, mucosal condition and clearance mechanisms [4].

### 2.2 Mucociliary clearance and formulation residence

Nasal mucus forms a dynamic protective layer over the epithelium. Ciliary movement continuously transports mucus and trapped particles. Conventional aqueous solutions may therefore have a short residence time. A formulation intended to remain at the nasal surface must be designed to interact with mucus without disrupting normal mucociliary function. Excessive viscosity or strong adhesion may be counterproductive if it interferes with distribution, comfort or clearance.

### 2.3 Thiolated chitosan as a mucoadhesive polymer

Chitosan is a cationic polysaccharide containing amino and hydroxyl groups that can contribute to interactions with mucosal surfaces.

Thiolated derivatives, often described as thiomers, introduce thiol groups that can form covalent disulfide bonds with cysteine-rich domains of mucin. Hydrogen bonding, electrostatic interactions and chain interpenetration may also contribute to adhesion. Thiomers

have been investigated as a class of mucoadhesive materials because of their potential to increase contact with mucosal tissues [6].

The concentration of polymer can influence the rheological and adhesive properties of a formulation. Increasing polymer concentration may increase viscosity and detachment force, but an excessive concentration may compromise handling, sprayability, spreading or drug release. Therefore, formulation optimization should consider multiple quality attributes rather than maximizing a single response.

### 2.4 Nanoemulsions in drug delivery

Nanoemulsions are kinetically stable dispersions of two immiscible liquids, typically oil droplets dispersed in an aqueous continuous phase and stabilized by surfactants. They can improve the apparent solubilization of selected compounds and provide a flexible platform for topical or mucosal delivery. Their performance depends on composition, droplet size distribution, interfacial properties and manufacturing conditions [7]. In the present formulation, oleic acid, Tween 80 and PEG 400 were selected as the oil, surfactant and co-surfactant components, respectively.

## 3. AIM AND OBJECTIVES

### 3.1 Aim

To formulate and evaluate a mucoadhesive intranasal nanoemulsion containing midodrine hydrochloride using thiolated chitosan as the mucoadhesive polymer, and to identify a formulation with a balanced physicochemical, release and mucoadhesive profile.

### 3.2 Specific objectives

1. To characterize midodrine hydrochloride by melting-point determination, solubility assessment, UV calibration and FTIR analysis.
2. To assess the compatibility of midodrine hydrochloride with the selected formulation excipients using FTIR spectroscopy.
3. To prepare six nanoemulsion batches containing increasing concentrations of thiolated chitosan (0.1 –0.6% w/v).
4. To evaluate the prepared formulations for visual appearance, pH, viscosity and drug content.
5. To determine in-vitro drug-release behaviour under controlled dissolution conditions.
6. To assess mucoadhesive strength using excised porcine nasal mucosa.
7. To examine the surface morphology of the selected formulation and identify the formulation with the most balanced measured attributes.

### 3.3 Study design and scope

The investigation was designed as a comparative formulation-development study involving six batches that differed in thiolated chitosan concentration while the nominal concentrations of drug, oil, surfactant and co-surfactant were held constant. Measurements were reported as mean ± standard deviation for three determinations where indicated. The study endpoints were limited to the in-vitro and ex-vivo tests described in the experimental record. No clinical, pharmacokinetic or in-vivo efficacy conclusions are drawn.

The primary optimization decision was based on the combined interpretation of drug content, pH, viscosity, mucoadhesive strength and in-vitro release. F5 was selected because it achieved the highest reported drug content and a mucoadhesive force close to the maximum measured value, while maintaining lower viscosity than F6.

## MATERIALS

### 4.1 Active pharmaceutical ingredient

Midodrine hydrochloride was used as the active pharmaceutical ingredient. The material was characterized before formulation by melting-point determination, solubility assessment, UV spectrophotometric calibration and FTIR spectroscopy. The experimental record reports a melting point of 201 °C.

### 4.2 Excipients

Oleic acid was used as the oil phase, Tween 80 as the non-ionic surfactant, PEG 400 as the co-surfactant and thiolated chitosan as the mucoadhesive polymer. Purified water was used as the aqueous phase. The excipient concentrations were maintained across the six formulations except for the concentration of thiolated chitosan.

### 4.3 Instruments and analytical equipment

The reported analytical equipment included a melting-point apparatus, UV-visible spectrophotometer, Fourier-transform infrared spectrophotometer, calibrated pH meter, rotational viscometer, scanning electron microscope, dissolution apparatus and texture analyser. Instrument calibration and suitability should be documented in the underlying laboratory records in accordance with the applicable quality system.

### 4.4 Reagents and media

Phosphate-buffered saline adjusted to pH 6.4 was used as the in-vitro release medium. The dialysis membrane was used as the diffusion barrier for release testing. Freshly excised porcine nasal mucosa was used for the mucoadhesion assessment.

### 4.5 General considerations

All materials should be handled according to their safety data sheets and institutional procedures. The formulation and analytical work should be performed using suitable laboratory controls, documented weighing records and calibrated instruments. The exact grade, batch number and certificate-of-analysis details of materials are not reproduced in this manuscript; these details may be retained in the study file and supplied if requested by the journal or reviewers.

## 5. PREFORMULATION STUDIES

### 5.1 Melting-point determination

The melting point of midodrine hydrochloride was determined by the capillary method. A suitable quantity of the powdered drug was introduced into a capillary tube and heated under controlled conditions using a melting-point apparatus. The observed melting point was recorded and compared with the expected range as a preliminary identity-related characterization test. The measured value was 201 °C.

### 5.2 Solubility assessment

Excess drug was added separately to water and selected candidate excipients. Samples were allowed to equilibrate, and undissolved material was removed by centrifugation or filtration. The concentration of dissolved drug in the clarified phase was determined by UV spectrophotometry using the established calibration relationship. The results were used to guide selection of the aqueous phase, oil phase, surfactant and co-surfactant.

### 5.3 UV spectrophotometric calibration

A series of midodrine hydrochloride standard solutions covering 10–90 µg/mL was prepared. Absorbance was measured at the analytical wavelength selected for the drug, and the relationship between concentration and absorbance was evaluated by linear regression. The reported calibration equation was $y = 0.0088x + 0.0050$, with a coefficient of determination ($R^2$) of 0.9996.

### 5.4 FTIR compatibility assessment

FTIR spectra of midodrine hydrochloride and the physical mixture containing the selected excipients were compared. Characteristic absorption bands were identified and assessed for shifts, disappearance or appearance of additional bands. The analysis was interpreted as a preliminary compatibility screen. FTIR alone cannot establish long-term chemical stability or exclude all possible drug–excipient interactions; additional stability-indicating testing would be required for a comprehensive compatibility assessment.

### 5.5 Selection of formulation components

The excipient selection was based on the reported solubility observations and the intended oil-in-water system.

Oleic acid was selected as the oil phase, Tween 80 as surfactant and PEG 400 as co-surfactant. The polymer concentration was varied systematically to examine its effect on the measured formulation attributes.

## 6. FORMULATION DEVELOPMENT

### 6.1 Formulation composition

Six formulations (F1–F6) were prepared with a fixed concentration of midodrine hydrochloride and fixed concentrations of the oil, surfactant and co-surfactant. Thiolated chitosan was incorporated at concentrations from 0.1 to 0.6% w/v. Purified water was added in a quantity sufficient to obtain the final formulation volume.

**Table 1:** ***Composition of midodrine hydrochloride nanoemulsions (% w/v)***

| Ingredient | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Midodrine hydrochloride | 1 | 1 | 1 | 1 | 1 | 1 |
| Oleic acid | 5 | 5 | 5 | 5 | 5 | 5 |
| Tween 80 | 20 | 20 | 20 | 20 | 20 | 20 |
| PEG 400 | 10 | 10 | 10 | 10 | 10 | 10 |
| Thiolated chitosan | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 |
| Purified water | q.s. 100 | q.s. 100 | q.s. 100 | q.s. 100 | q.s. 100 | q.s. 100 |

### 6.2 Preparation procedure

The oil phase was prepared by mixing oleic acid with the surfactant and co-surfactant. Midodrine hydrochloride was incorporated into the selected phase under mixing. Purified water was added gradually with continuous agitation to produce a coarse emulsion. The dispersion was subsequently subjected to high-energy emulsification to obtain the nanoemulsion system.

Thiolated chitosan was hydrated in the aqueous medium and added gradually to the respective formulation under controlled stirring to achieve the target polymer concentration. The batches were allowed to equilibrate and were examined visually for homogeneity and evidence of phase separation. The formulations were designated F1 through F6 in ascending order of polymer concentration.

### 6.3 Formulation coding

F1 contained 0.1% w/v thiolated chitosan; F2 contained 0.2%; F3 contained 0.3%; F4 contained 0.4%; F5 contained 0.5%; and F6 contained 0.6%. This design enabled evaluation of the effect of polymer concentration while maintaining the nominal levels of the other formulation components.

## 7.. EVALUATION METHODS

### 7.1 Visual appearance and homogeneity

Each formulation was inspected visually for colour, uniformity, visible particulate matter, creaming and phase separation. The six batches were described as uniform, milky-white dispersions without visible phase separation at the time of evaluation.

### 7.2 pH measurement

The pH meter was calibrated using appropriate standard buffers before use. A suitable quantity of each formulation was transferred to a clean vessel, and the pH was measured under consistent conditions. Measurements were performed in triplicate and expressed as mean ± standard deviation.

### 7.3 Viscosity measurement

Viscosity was measured using a rotational viscometer. The sample was allowed to equilibrate before measurement, and readings were obtained under the selected instrument conditions.

### 7.4 Drug-content determination

An accurately measured quantity of formulation equivalent to 10 mg of midodrine hydrochloride was extracted and diluted with a suitable solvent. The resulting solution was analysed by UV spectrophotometry against the calibration curve. Drug content was calculated as a percentage of the nominal amount present in the formulation. Each formulation was analysed in triplicate.

### 7.5 In-vitro drug-release study

In-vitro release was assessed using a dialysis membrane in a USP type II dissolution apparatus. The release medium consisted of 900 mL phosphate-buffered saline at pH 6.4, maintained at 37 ± 0.5 °C and stirred at 50 rpm. A quantity of formulation equivalent to 10 mg of midodrine hydrochloride was used. Samples of 5 mL were withdrawn at 0.5, 1, 2, 3, 4, 6, 8 and 12 h and replaced with equal volumes of fresh medium. Samples were filtered through a 0.45-µm membrane and analysed by UV spectrophotometry.

### 7.6 Mucoadhesive strength

Mucoadhesive strength was assessed using freshly excised porcine nasal mucosa and a texture analyser. The maximum detachment force required to separate

the formulation from the mucosal surface was recorded. The reported output was expressed in newtons.

### 7.7 Surface morphology

The morphology of the selected formulation was examined by scanning electron microscopy after drying. The reported micrograph was acquired at 6000× magnification. As the specimen was dried before imaging, the micrograph is interpreted as a surface-morphology observation and not as a direct measurement of liquid-state nanoemulsion droplet size.

## RESULTS

### 8.1 Preformulation characterization

Midodrine hydrochloride exhibited a melting point of 201 °C. The reported solubility in water was 94.62 ± 2.15 mg/mL. Among the formulation excipients, the measured solubility was highest in PEG 400 (56.30 ± 1.76 mg/mL), followed by Tween 80 (42.60 ± 1.43 mg/mL) and oleic acid (18.45 ± 0.94 mg/mL). The drug was described as soluble in methanol, slightly soluble in ethanol and poorly soluble in chloroform.

**Table 2:** ***Reported solubility of midodrine hydrochloride in selected media***

| Medium / excipient | Reported solubility (mg/mL) | Observation |
|---|---|---|
| Water | 94.62 ± 2.15 | Highest measured solubility |
| PEG 400 | 56.30 ± 1.76 | Selected co-surfactant |
| Tween 80 | 42.60 ± 1.43 | Selected surfactant |
| Oleic acid | 18.45 ± 0.94 | Selected oil phase |
| Methanol | Not quantified | Soluble |
| Ethanol | Not quantified | Slightly soluble |
| Chloroform | Not quantified | Poorly soluble |

The calibration curve was linear over the concentration range of 10–90 µg/mL. The regression equation was y = 0.0088x + 0.0050 and the coefficient of determination was 0.9996. This indicates a strong linear relationship within the reported range. Full analytical validation, including accuracy, precision, specificity and robustness, was not included in the available experimental summary.

### 8.2 FTIR analysis

The principal FTIR bands of midodrine hydrochloride were observed at 3363.00 $cm^{-1}$ (N–H stretching), 1681.98 $cm^{-1}$ (C=O stretching), 1602.90 $cm^{-1}$ (N–H bending) and 1249.91 $cm^{-1}$ (C–N stretching). In the physical mixture, the corresponding bands were observed at 3316.21, 1653.06, 1602.31 and 1247.02 $cm^{-1}$, respectively. No characteristic band was reported to disappear, and no new band was reported to appear.

**Table 3:** ***Characteristic FTIR bands of midodrine hydrochloride and its physical mixture***

| Functional group | Midodrine HCl ($cm^{-1}$) | Physical mixture ($cm^{-1}$) |
|---|---|---|
| N–H stretching | 3363.00 | 3316.21 |
| C=O stretching | 1681.98 | 1653.06 |
| N–H bending | 1602.90 | 1602.31 |
| C–N stretching | 1249.91 | 1247.02 |

The shifts in the N–H stretching and carbonyl bands may be consistent with non-covalent interactions, including hydrogen bonding, between the drug and formulation components. The FTIR findings support the absence of an obvious incompatibility signal under the conditions tested; they should not be interpreted as definitive proof of chemical stability.

### 8.3 PHYSICOCHEMICAL CHARACTERISTICS

All six formulations were reported as uniform, milky-white dispersions without visible phase separation. As the concentration of thiolated chitosan increased from 0.1 to 0.6% w/v, the pH decreased from 5.82 to 5.57. Over the same concentration range, viscosity increased from 18.42 to 41.38 cP. Drug content increased from

93.10% in F1 to a maximum of 98.60% in F5, followed by a slight decrease to 97.80% in F6.

**Table 4:** ***Physicochemical properties and mucoadhesive strength of formulations (mean ± SD, n = 3)***

| Batch | Thiolated chitosan (% w/v) | pH | Viscosity (cP) | Drug content (%) | Mucoadhesive strength (N) |
|---|---|---|---|---|---|
| F1 | 0.1 | 5.82 ± 0.04 | 18.42 ± 0.36 | 93.10 ± 1.20 | 0.184 ± 0.012 |
| F2 | 0.2 | 5.76 ± 0.03 | 21.76 ± 0.42 | 94.50 ± 1.00 | 0.236 ± 0.015 |
| F3 | 0.3 | 5.71 ± 0.04 | 25.83 ± 0.51 | 96.20 ± 0.90 | 0.291 ± 0.014 |
| F4 | 0.4 | 5.68 ± 0.03 | 30.64 ± 0.47 | 97.40 ± 0.80 | 0.348 ± 0.017 |
| F5 | 0.5 | 5.65 ± 0.02 | 35.72 ± 0.55 | 98.60 ± 0.60 | 0.426 ± 0.019 |
| F6 | 0.6 | 5.57 ± 0.04 | 41.38 ± 0.62 | 97.80 ± 0.70 | 0.451 ± 0.021 |

### 8.4 Visual appearance

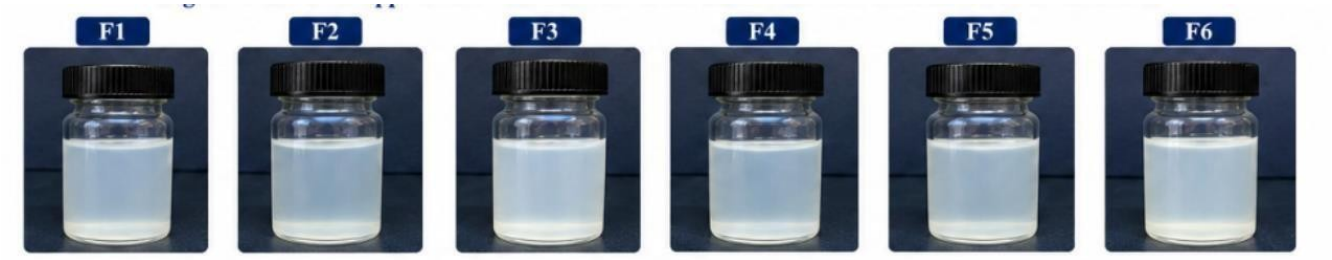



**Figure 1:** ***Visual appearance of formulations F1–F6.***

The visual inspection did not identify visible phase separation in the six formulations at the time of observation. This assessment is qualitative and does not replace instrumental evaluation of droplet size, polydispersity, zeta potential or physical stability.

### 8.5 MUCOADHESIVE STRENGTH AND IN-VITRO RELEASE

#### 8.5.1 Mucoadhesive strength

Mucoadhesive strength increased progressively with polymer concentration, from 0.184 ± 0.012 N for F1 to 0.451 ± 0.021 N for F6. F5 showed a detachment force of 0.426 ± 0.019 N, which was close to the highest value observed for F6. The increase is consistent with a greater availability of polymer functional groups and stronger interactions between the formulation and mucosal surface. However, the exact contribution of thiol-mediated covalent bonding was not directly measured in this study.

#### 8.5.2 In-vitro release profile

All formulations were described as exhibiting an initial faster release phase followed by a slower release phase over the 12-h test period. The reported cumulative release at 12 h was 98.16% for F1, 94.28 ± 1.18% for F5 and 96.84% for F6. For F5, the reported cumulative release values included 18.42 ± 0.86% at 0.5 h, 46.83% at 2 h, 78.65% at 6 h and 94.28 ± 1.18% at 12 h. The available record does not provide complete numerical release data with variability for every formulation and time point.

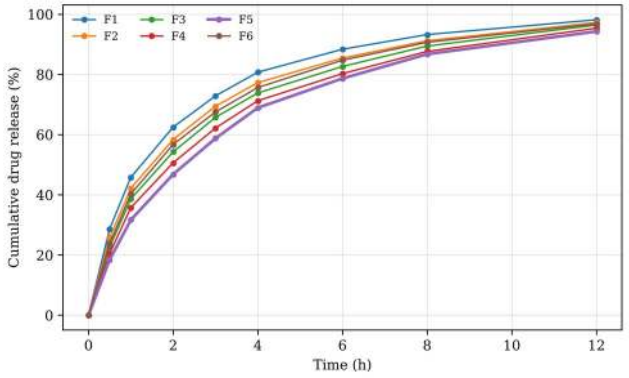



**Figure 2:** ***In-vitro release profiles of midodrine from formulations F1–F6, as provided in the experimental record.***

The lower cumulative release reported for F5 relative to F1 is consistent with increased diffusional resistance in a more structured polymer-containing system. The

differences in terminal release among formulations were modest. Statistical comparisons between batches were not reported; therefore, differences should be interpreted descriptively rather than as statistically significant effects.

### 8.6 MORPHOLOGICAL EVALUATION AND FORMULATION SELECTION

#### 8.6.1 Surface morphology

The selected formulation, F5, was examined by scanning electron microscopy after drying. The micrograph showed rounded surface features with a relatively smooth appearance and limited visible aggregation at the reported magnification. Since the sample was dried before imaging, the observed structures cannot be used to determine the size distribution of droplets in the original liquid nanoemulsion.

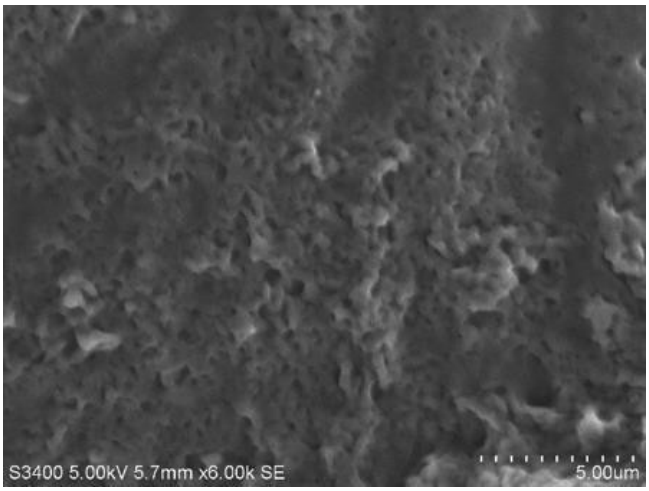



**Figure 3:** ***Scanning electron micrograph of the selected formulation F5 (reported magnification: 6000×).***

#### 8.6.2 Selection of F5

F5, containing 0.5% w/v thiolated chitosan, was selected as the optimized formulation based on the combined measured attributes. It showed the highest drug content (98.60 ± 0.60%), a pH of 5.65 ± 0.02 and a viscosity of 35.72 ± 0.55 cP. Its mucoadhesive strength (0.426 ± 0.019 N) was close to the maximum measured value for F6 (0.451 ± 0.021 N), while its viscosity was lower than that of F6 (35.72 versus 41.38 cP). F5 also showed the lowest reported cumulative release among the tested formulations at 12 h.

The selection therefore reflects a compromise between mucoadhesion, viscosity, drug content and release behaviour. F6 provided the highest detachment force but also the highest viscosity and a lower drug content than F5. The available data do not establish that F5 is superior in nasal delivery performance, because spray characteristics, droplet size, permeation, mucosal tolerability and in-vivo response were not evaluated.

## DISCUSSION

The study explored the effect of thiolated chitosan concentration on the properties of midodrine hydrochloride nanoemulsions intended for intranasal administration. The results indicate that increasing polymer concentration was associated with a gradual increase in viscosity and mucoadhesive strength. These trends are consistent with the expected contribution of polymer-chain entanglement and mucin interactions to the rheological and adhesive properties of chitosan-based systems. Thiolated polymers have been described as mucoadhesive materials capable of interacting with mucosal glycoproteins through several mechanisms, including disulfide formation [6].

The observed pH values ranged from 5.57 to 5.82. The modest decrease with increasing polymer concentration may reflect the ionizable functional groups of the polymer. Nasal formulation pH should be considered together with buffering capacity, osmolality, excipient tolerability and the potential effect on ciliary function. pH alone is insufficient to establish nasal compatibility.

Drug content was highest in F5 and decreased slightly in F6. This non-linear pattern suggests that increasing polymer concentration does not necessarily improve all formulation attributes. The increase in viscosity may influence mixing, extraction efficiency or drug distribution; however, the available data do not establish the mechanism. Additional content-uniformity and extraction-recovery studies would help clarify the observation.

The release profiles were described as biphasic, with a faster initial phase and slower subsequent release. F5 showed 94.28 ± 1.18% cumulative release at 12 h. The polymer may increase diffusional resistance and thereby moderate drug release. Nevertheless, a 12-h in-vitro release experiment does not establish the onset or

duration of systemic pharmacological action after nasal administration. The relationship between in-vitro release and in-vivo absorption must be demonstrated experimentally.

Nanoemulsions have been investigated as adaptable drug-delivery systems, with their performance dependent on composition and droplet characteristics [7]. In this study, the formulation was described as a nanoemulsion, but no direct droplet-size distribution, polydispersity index or zeta-potential results were available. These are important attributes for confirming the colloidal characteristics and physical stability of the system.

Overall, F5 appears to be the most balanced candidate among the six formulations based on the reported endpoints. The results provide a basis for further development but should be interpreted as preliminary formulation findings rather than evidence of clinical suitability.

## 10. STUDY LIMITATIONS, CONCLUSION AND DECLARATIONS

### 10.1 Study limitations

Several limitations should be considered when interpreting the findings. First, droplet size, polydispersity index and zeta potential were not reported, so the nanoscale characteristics and colloidal stability of the dispersion remain to be confirmed.

### 10.2 Conclusion

Mucoadhesive nanoemulsions containing midodrine hydrochloride and thiolated chitosan were prepared and evaluated. Increasing thiolated chitosan concentration was associated with increased viscosity and mucoadhesive strength and a modest reduction in pH. Among the six formulations, F5 containing 0.5% w/v thiolated chitosan provided the most balanced profile, with drug content of 98.60 ± 0.60%, pH 5.65 ± 0.02, viscosity 35.72 ± 0.55 cP, mucoadhesive strength 0.426 ± 0.019 N and cumulative in-vitro release of 94.28 ± 1.18% at 12 h.

### 10.3 Acknowledgements

The authors gratefully acknowledge the institutional facilities and departmental support provided for the successful completion of this research work.

### 10.4 Funding

No external funding was received for this research.

### 10.5 Conflict of Interest

The authors declare that there are no competing financial or non-financial interests that could have influenced the research, authorship, or publication of this manuscript.

### 10.6 Ethics Statement

The study involved the use of freshly excised porcine nasal mucosa for ex-vivo mucoadhesive strength evaluation. The applicable ethical approval or exemption status was determined in accordance with institutional guidelines.

### 10.7 Author Contributions

All authors contributed to the research work, manuscript preparation, critical revision, and approval of the final version of the manuscript.

### 10.8 Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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HOW TO CITE: Elangovan S., Uma Maheshwari P. V., Krishnamoorthy B., Perumal P., Formulation and Evaluation of Mucoadhesive Intranasal Midodrine-Loaded Nanoemulsion for the Management of Hypotension, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 5768-5777. https://doi.org/10.5281/zenodo.24583429