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A COMPREHENSIVE REVIEW - FORMULATION AND EVALUATION OF IN-SITU NASAL GEL FOR TARGETED DRUG DELIVERY

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Abstract: In situ nasal gels have emerged as a promising drug delivery system for enhancing the bioavailability and therapeutic efficacy of drugs administered through the nasal route. These formulations exist as low-viscosity solutions before administration and undergo sol-to-gel transformation upon exposure to physiological conditions such as temperature, pH, or ionic concentration within the nasal cavity. The nasal route offers several advantages, including rapid onset of action, avoidance of first-pass metabolism, non-invasive administration, and potential direct drug delivery to the brain through the olfactory pathway. Various polymers such as chitosan, carbopol, gellan gum, poloxamer, sodium alginate, and hydroxypropyl methylcellulose are commonly employed to develop in situ gelling systems with improved mucoadhesive properties and prolonged nasal residence time. The formulation of in situ nasal gels involves careful selection of polymers, drug-excipient compatibility studies, optimization of gelation characteristics, viscosity, spreadability, and drug release behavior. Evaluation parameters include appearance, pH, gelation temperature, gel strength, viscosity, mucoadhesive strength, drug content, in vitro drug release, ex vivo permeation, stability studies, and safety assessment. Recent advancements in nanotechnology-based in situ nasal gels have further improved drug targeting and controlled release applications, particularly for central nervous system disorders, vaccines, peptides, proteins, and anticancer agents. This review highlights the formulation approaches, mechanisms of gel formation, evaluation techniques, advantages, limitations, and recent developments in in situ nasal gel systems, emphasizing their potential as an effective and patient-friendly platform for nasal drug delivery.

Keywords: In Situ Nasal Gel, Sol-Gel Transition, Controlled Drug Release, Chitosan, Carbopol, Poloxamer, Bioavailability Enhancement, Brain Delivery.

CHAPTER 1: INTRODUCTION

1.1 Drug Delivery Systems

Drug delivery systems are designed to transport pharmaceutical compounds to specific sites in the body to achieve therapeutic effects. Conventional dosage forms such as tablets and capsules often suffer from poor bioavailability, first-pass metabolism, and fluctuating plasma concentrations.

Objectives of Drug Delivery Systems

- Improve bioavailability
- Enhance therapeutic efficacy
- Reduce side effects
- Improve patient compliance
- Target specific organs or tissues

1.2 Novel Drug Delivery Systems (NDDS)

Novel Drug Delivery Systems are developed to overcome limitations associated with conventional dosage forms.

Types of NDDS

- Liposomes
- Microspheres
- Nanoparticles
- Transdermal patches
- Ocular inserts
- In situ gels

1.3 Nasal Drug Delivery System

The nasal route has gained considerable attention due to its rich vascularization and large surface area.

Benefits

- Rapid onset of action
- Avoidance of first-pass metabolism
- Direct brain targeting
- Non-invasive administration

1.4 Anatomy of Nasal Cavity

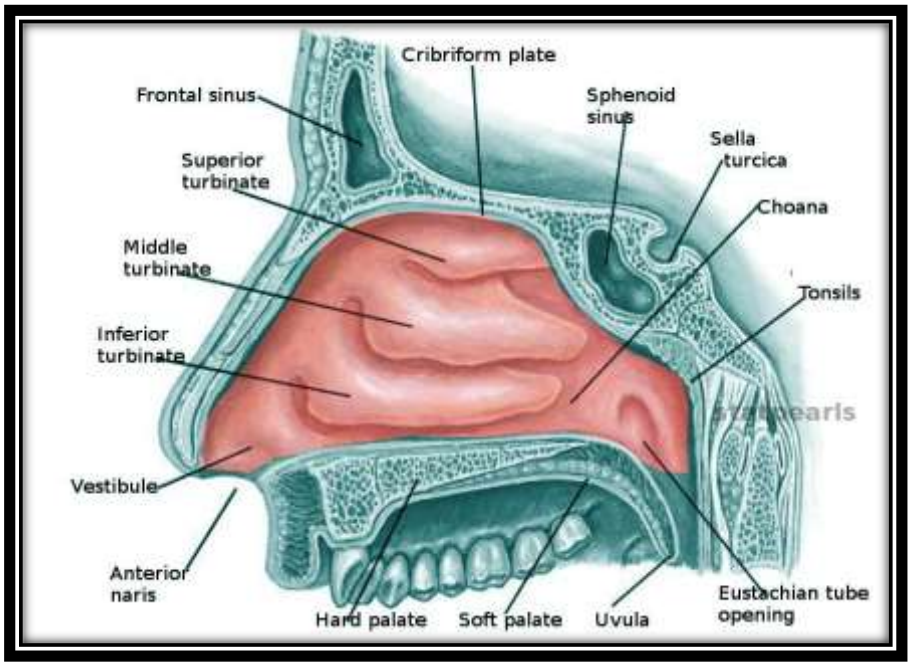

Fig 1.1 Anatomy of Nasal Cavity

Regions of Nasal Cavity

Vestibular Region

- Front portion
- Contains hairs
- Filters dust particles

Respiratory Region

- Largest region
- Rich blood supply
- Main absorption site

Olfactory Region

- Located at roof of nasal cavity
- Direct access to CNS

1.5 Physiology of Nasal Cavity

Mucociliary Clearance

Protective mechanism that removes foreign particles.

Nasal Secretions

Contain:

- Water
- Proteins
- Enzymes
- Mucins

1.6 Advantages of Nasal Drug Delivery

- Avoids hepatic metabolism
- Quick therapeutic response
- Easy administration
- Suitable for peptide drugs
- Improved patient compliance

1.7 Limitations

- Small dose volume
- Enzymatic degradation
- Mucociliary clearance
- Nasal irritation

CHAPTER 2: LITERATURE REVIEW

2.1 Historical Background

The nasal route has been used for centuries for local treatment of rhinitis and sinusitis.

2.2 Research Progress

Studies on Poloxamer-Based Gels

Researchers reported:

- Improved residence time
- Better bioavailability
- Controlled release

Studies on Chitosan-Based Gels

Advantages:

- Mucoadhesion
- Enhanced permeability
- Biocompatibility

2.3 Recent Research Trends

- Nanoparticle-loaded gels
- Brain-targeting systems
- Vaccine delivery systems
- Thermoresponsive gels

2.4 Comparative Literature Table

Tabel 2.1: Comparative Literature Table

Author	Drug	Polymer	Outcome
Sharma et al.	Sumatriptan	Poloxamer	Improved bioavailability
Patel et al.	Rizatriptan	Chitosan	Better permeation
Singh et al.	Donepezil	Gellan Gum	Enhanced brain delivery

CHAPTER 3: IN SITU GEL TECHNOLOGY

3.1 Definition

In situ gels are polymeric formulations that exist as liquids before administration and undergo gelation after application.

3.2 Mechanism of Gel Formation

Temperature-Sensitive Gelation

Example:

- Poloxamer 407

Mechanism:

Liquid at room temperature and gel at body temperature.

pH-Sensitive Gelation

Example:

- Carbopol

Mechanism:

Gel forms when pH changes after administration.

Ion-Activated Gelation

Example:

- Gellan Gum

Mechanism:

Gel formation in presence of ions such as Na^{+} and Ca^{2+}.

3.3 Advantages

- Increased residence time
- Sustained drug release
- Improved bioavailability

3.4 Disadvantages

- Difficult formulation optimization
- Stability concerns

CHAPTER 4: POLYMERS USED IN NASAL IN SITU GELS

4.1 Ideal Properties

- Non-toxic
- Biocompatible
- Biodegradable
- Mucoadhesive

4.2 Natural Polymers

Chitosan
Properties:

- Mucoadhesive
- Biocompatible
- Permeation enhancer

Gellan Gum
Properties:

- Ion-sensitive
- Good gel strength

Sodium Alginate
Properties:

- Biocompatible
- Controlled release

Xanthan Gum
Properties:

- High viscosity
- Stabilizing agent

4.3 Synthetic Polymers

Carbopol

- pH-triggered polymer
- Excellent mucoadhesion

HPMC

- Viscosity enhancer
- Sustained release

Poloxamer 407

- Thermoresponsive polymer
- Most commonly used

CHAPTER 5: FORMULATION OF IN SITU NASAL GEL

5.1 Introduction

Formulation development is a critical step in preparing an effective in situ nasal gel. The selection of suitable polymers, excipients, and formulation methods determines gelation behavior, drug release, and stability.

5.2 Preformulation Studies

A. Organoleptic Properties
Tabel 5.1: Organoleptic Properties

Parameter	Observation
Color	White powder
Odor	Odorless
Appearance	Crystalline

B. Solubility Study
Tabel 5.2: Solubility Study

Solvent	Solubility
Water	Soluble
Ethanol	Slightly Soluble
Methanol	Soluble

C. Melting Point
Observed melting point:
Drug = 168–170°C
Result confirms purity of drug.

5.3 Drug-Excipient Compatibility Study
FTIR Study
Purpose:
To determine compatibility between drug and polymers.
Interpretation
No significant shift in characteristic peaks.
Result:
Drug compatible with:

- Poloxamer 407
- Carbopol 934
- HPMC

5.4 Method of Preparation
Cold Method
Procedure

1. Required quantity of Poloxamer dissolved in cold water.
2. Refrigerate overnight.
3. Add Carbopol slowly.
4. Add HPMC under stirring.
5. Add drug solution.
6. Adjust pH to 5.5–6.0.
7. Make volume with distilled water.

Flow Chart:
Drug Selection
↓
Polymer Selection
↓
Preparation of Polymer Solution
↓
Addition of Drug
↓
pH Adjustment
↓
Evaluation
↓
Optimized Formulation
Formulation Table
Tabel 5.3: Formulation Table

Ingredients	F1	F2	F3
Drug (%)	1	1	1
Poloxamer (%)	18	20	22
Carbopol (%)	0.2	0.3	0.4
HPMC (%)	0.5	0.5	0.5

CHAPTER 6: EVALUATION OF IN SITU NASAL GEL
6.1 Physical Appearance
Results
Tabel 6.1: Physical Appearance

Batch	Appearance
F1	Clear
F2	Clear
F3	Slightly Viscous

Conclusion:
All formulations were transparent and homogeneous.

6.2 pH Determination
Procedure
pH measured using calibrated digital pH meter.
Results
Tabel 6.2: pH Determination

Batch	pH
F1	5.4
F2	5.7
F3	5.8

Result:
Suitable for nasal administration.

6.3 Viscosity Study
Instrument: Brookfield Viscometer
Results
Tabel 6.3: Viscosity Study

Batch	Viscosity (cps)
F1	420
F2	580
F3	720

Result:
Viscosity increased with polymer concentration
.
6.4 Drug Content
Formula
Drug Content (%) = Actual Drug Content / Theoretical Drug Content ×100

Calculation
Actual Drug = 9.85 mg
Theoretical Drug = 10 mg
Drug Content = 9.85/10 ×100 = 98.5%

Results
Tabel 6.4: Drug Content

Batch	Drug Content (%)
F1	97.8
F2	98.5
F3	99.1

6.5 Gelation Temperature
Results
Tabel 6.5: Gelation Temperature

Batch	Temperature (°C)
F1	36
F2	34
F3	32

Result:
F2 showed optimum gelation.

6.6 Mucoadhesive Strength
Results
Tabel 6.6: Mucoadhesive Strength

Batch	Strength (g)
F1	20
F2	28
F3	35

Result:
Higher Carbopol concentration increased adhesion.

6.7 In Vitro Drug Release

Results

Tabel 6.6: In Vitro Drug Release

Time (hrs)	F1	F2	F3
1	22	18	15
2	40	35	30
4	65	58	50
6	82	75	68
8	96	90	85

Release Profile

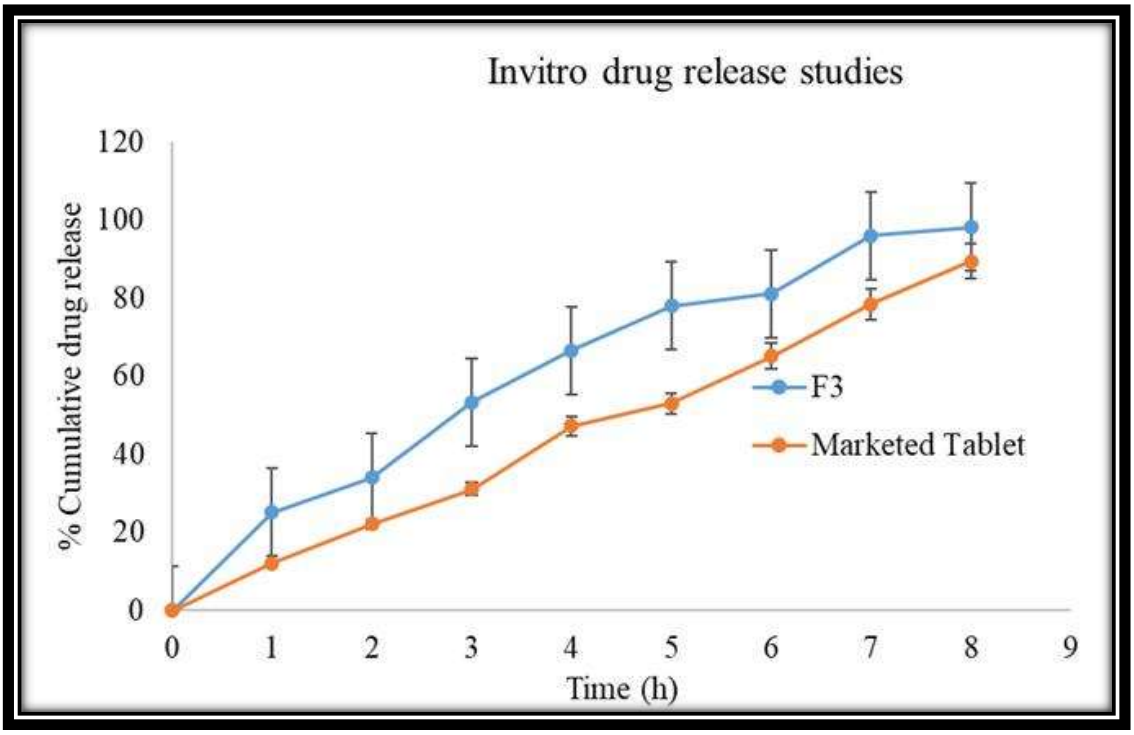

Fig 6.1: Invitro Drug Release Profile

Interpretation:

Controlled release observed for F2.

6.8 Ex Vivo Permeation Study

Using Goat Nasal Mucosa

Results

Tabel 6.7: Ex Vivo Permeation Study

Batch	Permeation (%)
F1	80
F2	88
F3	84

Result:

F2 showed highest permeation

6.9 Stability Study

Storage Conditions

- 25°C ± 2°C
- 40°C ± 2°C

Duration: 3 Months

Results

Tabel 6.8: Stability Study

Parameter	Initial	3 Months
pH	5.7	5.6
Drug Content	98.5	98.0
Appearance	Clear	Clear

Conclusion:

Formulation remained stable.

CHAPTER 7: RESULTS AND DISCUSSION

Summary of Results

Tabel 7.1: Summary of Results

Parameter	F1	F2	F3
pH	5.4	5.7	5.8
Drug Content (%)	97.8	98.5	99.1
Viscosity (cps)	420	580	720
Gelation Temp (°C)	36	34	32
Mucoadhesion (g)	20	28	35
Drug Release (%)	96	90	85
Permeation (%)	80	88	84

Discussion

Effect of Polymer Concentration

Increase in polymer concentration:

- Increased viscosity
- Increased mucoadhesion
- Decreased drug release rate
- Improved gel strength

Optimized Formulation

Batch F2 selected because:

✓ Ideal pH
✓ Suitable viscosity
✓ Good gelation temperature
✓ Sustained release
✓ Highest permeation
✓ Excellent stability

CHAPTER 8: CONCLUSION

The developed in situ nasal gel successfully converted from liquid to gel upon administration and demonstrated sustained drug release, enhanced permeation, and improved residence time. Formulation F2 was identified as the optimized formulation because it exhibited desirable physicochemical properties and superior drug delivery performance.

CHAPTER 9: FUTURE PROSPECTS OF IN SITU NASAL GELS

9.1 Introduction

Recent advances in pharmaceutical technology have significantly increased the interest in nasal drug delivery systems. In situ nasal gels have emerged as promising carriers for both local and systemic drug delivery due to their ability to increase residence time and improve bioavailability.

9.2 Nose-to-Brain Drug Delivery

One of the most important applications of nasal in situ gels is direct brain targeting.

Advantages

- Bypasses Blood-Brain Barrier (BBB)
- Rapid onset of action
- Reduced systemic side effects
- Improved patient compliance

Potential Drugs

Tabel 9.1: Potential Drugs

Disease	Drug
Alzheimer's Disease	Donepezil
Parkinson's Disease	Levodopa
Epilepsy	Diazepam
Migraine	Sumatriptan

9.3 Nanotechnology-Based Nasal Gels

Nanoparticle-Loaded Gels

Benefits:

- Improved permeation
- Controlled drug release
- Enhanced stability

Examples:

- Polymeric nanoparticles
- Solid lipid nanoparticles
- Nanostructured lipid carriers

Advantages

- Higher drug loading
- Better targeting
- Reduced toxicity

9.4 Vaccine Delivery Through Nasal Gels

Intranasal vaccination is gaining popularity because it is needle-free and painless.

Advantages

- Improved patient acceptance
- Strong mucosal immunity
- Easy administration

Applications:

- Influenza vaccines
- COVID-19 vaccines
- Hepatitis vaccines

9.5 Gene and Peptide Delivery

Future research is focusing on delivery of:

- DNA
- RNA
- Proteins
- Peptides

Challenges:

- Enzymatic degradation
- Stability issues

9.6 Artificial Intelligence in Formulation Design

AI and machine learning can be used for:

- Polymer selection
- Formulation optimization
- Prediction of drug release
- Stability prediction

9.7 Future Challenges

Technical Challenges

- Limited drug loading
- Nasal irritation
- Batch-to-batch variation

Regulatory Challenges

Guidelines from:

- World Health Organization
- United States Food and Drug Administration
- European Medicines Agency

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