

Formulation and Evaluation of Naphazoline Nasal Spray

Lokesh Janardhan Sayam, Sayyad Faizan Sayyad Roshan, Shreya Ravindra Sarve,
Archana Kajale-kulkarni

B. Pharm final year student, Associate Professor

Department of Pharmaceutics, Yavatmal Zilla Vikas Samiti's Pataldhamal Wadhvani
College of Pharmacy, Yavatmal. Sant Gadge Baba Amravati University.

Abstract:

A nasal spray is a liquid medication delivered into the nasal cavity through a spray device for local or systemic therapeutic effects. It is a non-invasive drug delivery system that offers several advantages. Naphazoline is a topical sympathomimetic agent commonly formulated as ophthalmic or nasal preparations for its vasoconstrictive properties.

The formulation of Naphazoline generally includes suitable vehicles such as purified water, along with buffering agents to maintain physiological pH, preservatives like Methyl paraben, Isotonicity agent Sodium Chloride, Buffer Sodium Phosphate, Solvent PEG 400, Glycerine, to ensure microbial stability, and stabilizers to enhance shelf life. The drug acts by stimulating alpha-adrenergic receptors in the blood vessels, leading to vasoconstriction and reduced swelling.

All formulations (F1–F6) showed a clear solution appearance, indicating good solubility and absence of particulate matter. The pH values ranged from 6.0 to 6.5, which is close to physiological pH, suggesting that the formulations are suitable and less likely to cause irritation. F1, F5, and F6 showed a circular spray pattern (uniform distribution) whereas batches F2, F3 and F4 showed oblong spray pattern. The volume of each spray ranged from 0.9 ml to 1.2 ml. The percentage of drug release (time in minutes) decreased from F1 to F6. F1 showed the highest (50 min), F6 showed the lowest (10 min). Batch F6 can be considered optimized, as it gives immediate drug release, Suitable pH good spray pattern (circular), Acceptable viscosity and density and better drug release profile as compare to another batches.

Keywords: Nasal Spray, Nasal Cavity, Naphazoline, Epithelium, Buffer

1. Introduction:

Therapy through intranasal administration has been accepted as an important mode of treatment since ancient times. In recent years, many drugs have been shown to achieve better systemic bioavailability through the nasal route than by oral administration. The nasal cavity may be exploited as a route of entry into the systemic circulation, especially for those compounds that cannot be administered orally because they are destroyed in the gastrointestinal fluids or undergo extensive first-pass metabolism in the liver during their first passage around the circulation.[1] Nasal spray formulations are an increasingly popular method for delivering both local and systemic therapies. They are commonly used for treating conditions such as allergic rhinitis, nasal congestion, and more recently for systemic treatments like migraines and hormone replacement therapy.

The nasal route offers significant advantages, including rapid drug absorption due to the rich blood supply in the nasal mucosa, and the avoidance of first pass metabolism. These features make nasal sprays a convenient and effective option for patients.[2] Now a day's multiple types of formulation are used to administer drug by nasal route, which includes nasal spray, nasal drop, nasal powder, nasal gels and nasal insert etc. Administration of drugs through the nose in the spray dosage form is a non-invasive method that gives rapid onset of drug action. Because the nasals spray dosage form is cost-effective, easy to use/carry and self-administrable, it has high patient compliance. Therefore, nasal drug delivery has become a popular route of drug administration and has strong growth opportunity.[3]

The nasal delivery also appears to be a good approach to get over the barriers for blood brain barrier (BBB) that permits direct medication delivery the central nervous system active bio phase compounds. It has also been regarded as one of vaccination administration.[4] Nasal delivery is being paid consciousness and significance as optional dosage form. Nasal delivery system is retained as valuable way of drug delivery for topical as well as systemic therapies. The systemic delivery of drug molecules by nasal route offers advantages as high permeability, vasculature and low enzymatic environment.

Nasal spray: A nasal spray is a pharmaceutical dosage form in which a drug solution or suspension is administered into the nasal cavity in the form of a fine mist using a spray pump device.[5]

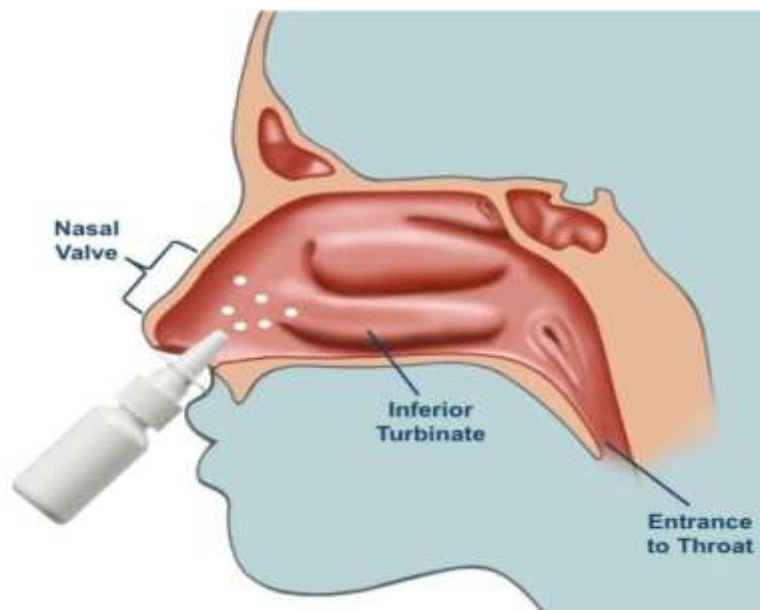


Fig 1. Introduction of nasal spray in nasal cavity [5]

Overall, nasal sprays provide targeted drug delivery, rapid onset of action, and better patient compliance, making them an effective and preferred dosage form for nasal disorders. This research paper focuses on the formulation and evaluation of Naphazoline nasal spray and highlights its clinical use in nasal decongestion.

Diseases related to Nasal Cavity

Allergic Rhinitis: Allergic rhinitis is an inflammation of the membranes lining the nose, often triggered by allergens such as pollen, dust mites, mold, or pet dander.

Symptoms: Sneezing, runny or congested nose, itchy eyes, postnasal drip, watery eyes, and fatigue. **Causes:** Immune system overreaction to allergens like pollen, dust mites, animal dander, mold, or certain foods.

Nasal Polyps: Nasal polyps are soft, painless, noncancerous growths that develop on the lining of the nasal passages or sinuses due to chronic inflammation.

Symptoms: Chronic nasal congestion, runny nose, postnasal drip, reduced or lost sense of smell, and facial pressure.

Causes: Chronic inflammation of the nasal mucosa due to asthma, allergies, or chronic sinus infections.[6]

Chronic Sinusitis: Chronic sinusitis is characterized by inflammation of the sinuses lasting 12 weeks or longer. It can result from infections, nasal polyps, or swelling of the sinus lining. **Symptoms:** Nasal congestion, facial pain or pressure, thick nasal discharge, reduced sense of smell, headache, and cough.

Causes: Infections (bacterial, viral, or fungal), nasal polyps, structural abnormalities (e.g. deviated septum), or persistent inflammation.[7]

Deviated Nasal Septum: A deviated septum occurs when the nasal septum, the cartilage and bone dividing the nasal cavity, is displaced to one side.

Symptoms: Nasal obstruction (difficulty breathing through one or both nostrils), frequent sinus infections, snoring, and nosebleeds.

Causes: Congenital (present from birth) or trauma to the nose causing displacement of the septum.[8]

Nasal Vestibulitis: Nasal vestibulitis is an infection of the nasal vestibule, often caused by bacteria like *Staphylococcus aureus*. It can lead to redness, swelling, and pain at the entrance of the nose.

Symptoms: Redness, swelling, pain at the entrance of the nose, crusting, and sometimes pus discharge.

Causes: Bacterial infection (commonly *Staphylococcus aureus*) in the nasal vestibule, often due to nose-picking or injury.[9]

Anatomy and Physiology of Nasal Cavity:

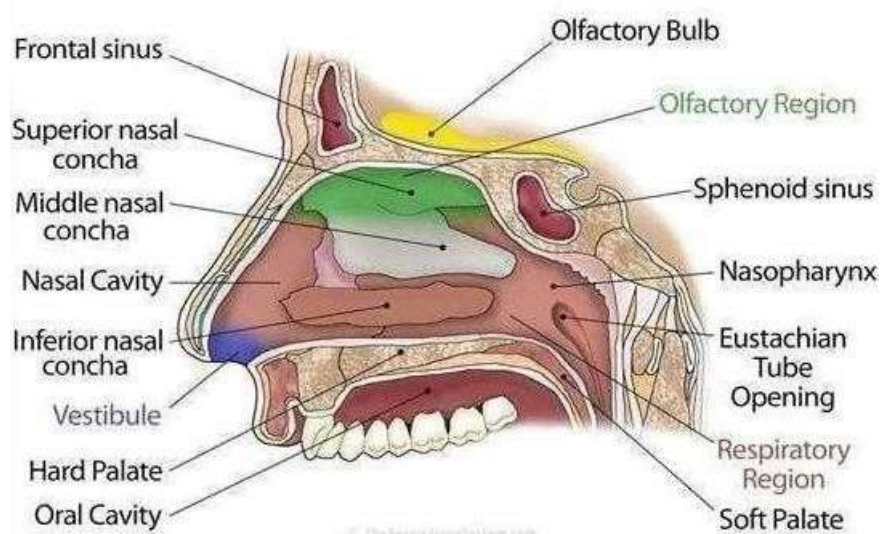


Fig 2: Anatomy and Physiology of nasal cavity.[10]

In humans and other animal species, the major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidifies the inhaled air before reaching the lowest airways. The human nasal cavity has a total volume of 1520 ml (about 51.4 oz) and a total surface

area of approximately 150 cm. The nose is separated in two nasal cavities by the septum. The volume of each cavity is about 7.5 ml (about 0.25 oz)

and has a surface area around 75 cm (about 2.46 ft) pH of the mucosal secretions ranges from 5.0 to 6.7 in children and to 6.5 in adults. The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min. From the nose, mucus moves at a rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min. [10]

Three regions can be distinguished in each part:

Nasal vestibule

In this area of nasal cavity, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at the same time, the absorption of substances including drugs becomes very difficult in this region.

Atrium

Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli.[11]

Respiratory region

It is divided in superior, middle and inferior turbinate's which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation of inhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. Nasal mucus is indispensable for several physiological functions, such as humidification and warming of the inhaled air, and also offers physical and enzymatic protection of the nasal epithelium against several foreign compounds, including drugs. The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins. Beneath of it, there is the lamina propria which is richly supplied with blood vessels, including many very permeable fenestrated capillaries, nerves, glands and immune cells. The last ones produce immunoglobulin an antibodies that confer immunological protection against bacteria and virus.[12]

Olfactory region

The olfactory region is located in the roof of the nasal cavity and extends a short way down the Septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception.[13]

Mechanism of drug absorption by nasal route.

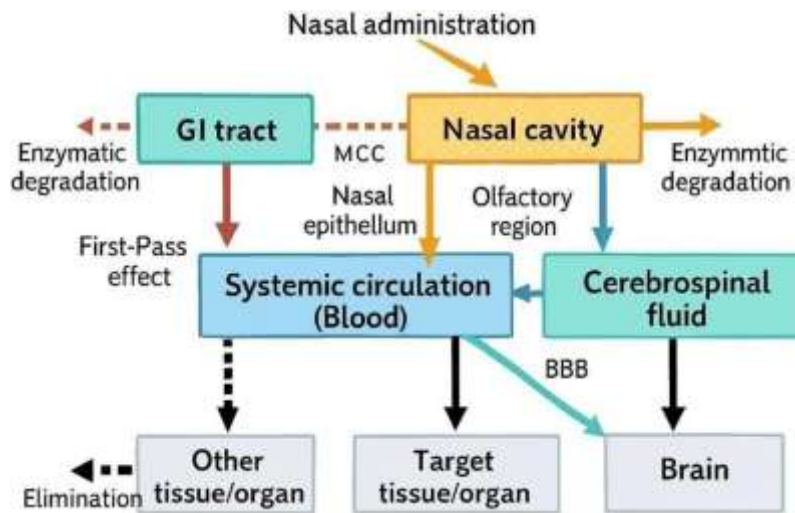


Fig 3 : Mechanism of drug absorption by nasal route [14] Table 1: Epithelial cells of nasal cavity [15]

Nasal Sections	Epithelial Characteristics Cells / Functions	Surface Area	Vascularization	Permeability
Vestibule	Stratified squamous and keratinized epithelial cells with nasal hairs / Support and protection	Columnar non ciliated cells / Support -Columnar ciliated cells / Support and muciliary clearance - Globet cells / Mucus secretion - Basal cells / Progenitors of other cell types	Low	Poor
Atrium	Stratified squamous cells / Support Pseudostratified cells / Support	NF	Low	Reduced
Respiratory Region	Columnar non ciliated cells / Support - Columnar ciliated cells / Support and muciliary clearance -Globet cells / Mucus secretion -Basal cells / Progenitors of other cell types	≈ 130 cm ²	Very high	Good

Olfactory Region	Sustentacular Support cells and synthetic -Olfactory receptor cells / Olfaction Perception -Basal cells / Progenitors of other cell Types	15 cm ²	High	Direct access to CNS
------------------	---	--------------------	------	----------------------

Advantages of nasal drug delivery system:

- Availability of large nasal mucosal surface area for dose absorption.
- Onset of action is rapid.
- Non-invasive and easy for administration.
- Bypass the BBB.
- Degradation of drug observed in GIT is avoided.
- Hepatic first pass metabolism is absent.
- Nasal bioavailability of small drug molecules is good.
- Bioavailability of large drug molecules can be increased by means of absorption enhancers.
- Unsuitable drug candidates for oral route can be successfully given via nasal route.[16]
- Convenient route for the patient on long term therapy.
- Improved bioavailability.
- Side effects are reduced due to low dose.
- Patient convenience and compliance is improved.
- A self-administration is possible.
- Direct transport into systemic circulation and CNS is Possible.
- Offers lower risk of overdose.[17]

Disadvantages:

- Delivery volume in nasal cavity is restricted to 25-200µL.
- High molecular weight compounds cannot be delivered through this route.
- Adversely affected by pathological conditions.
- Normal defence mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
- Irritation of nasal mucosa by drugs like Budesonide, Azilactine.
- Limited understanding of mechanisms and less developed models at this stage.
- Systemic toxicity occurring due to absorption enhancers is yet not established.
- Smaller absorption surface compared with GIT.
- Possibility of nasal irritation hence inconvenient compared with oral route.
- Enzymatic barrier to permeability of drug.[18]

Possible route of transport of nasal drug administration:

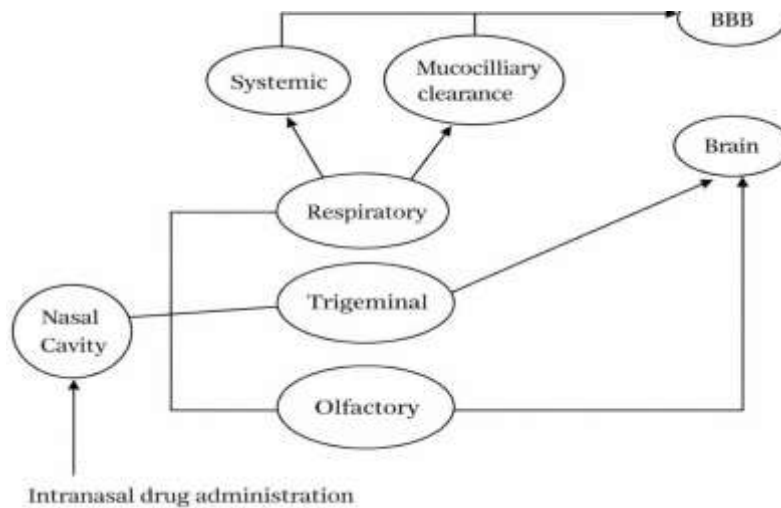


Fig 4. Possible route of transport of nasal drug administration.[19]

2. Literature Review:

1. **Lohare Rahul Sanjay *et.al*, (2025) [20]** : Evaluated that Oral Drug Delivery is widely preferred for its convenience, but unpleasant taste reduces patient acceptance, especially in children and the elderly. Taste-masking technologies improve palatability by using materials that complex or encapsulate drugs to prevent interaction with taste receptors. This review outlines different synthetic and natural taste-masking materials, their mechanisms, applications, evaluation methods, and related regulatory considerations.

2. **Shuhua Wei *et.al*, (2025) [21]**: Studied the drug transport routes and influencing factors for various diseases after nasal administration, and puts forward targeted strategies for enhancing the efficacy of precise delivery. Nasal drug administration constitutes an efficient and non-invasive modality of drug delivery. To elevate the drug absorption and delivery efficiency, it is of paramount importance to delineate the transport routes and their enhancement mechanisms.

3. **Letícia Apolinário Carlos da Silva *et.al*, (2024) [22]**: Analysed the risks and harmful effects associated with the use of Naphazoline Hydrochloride and focused on identifying the potential risks and adverse effects linked to NHC use. The findings highlighted that misuse and self-medication with NHC were common and posed significant public health concerns. Major harms associated with indiscriminate use included systemic adverse effects, rebound congestion, drug-induced rhinitis, and dependence.

4. **Nehad Jaser Ahmed *et.al*, (2021) [23]**: Evaluated the outpatient use of nasal Naphazoline in a public hospital in Alkharj. Over a 6-month period, 393 patients received naphazoline, predominantly young male adults aged 20–29 years. Most prescriptions were issued by resident doctors from the emergency department, with nasal drops being the most common formulation, either alone or combined with chlorpheniramine.

5. **Mirajkar Reshma Nilesh *et.al*, (2021) [24]**: Stated that taste played an important role in oral drug formulation, and bitter taste was a common challenge that affected patient compliance. The review also discussed factors influenced the selection of taste-masking techniques and methods used to evaluate their effectiveness. These approaches worked

by either preventing the drug from interacting with taste receptors or modifying its release in the oral cavity.

6. **Sulaiman Alnasser *et.al***, (2019) ^[25]: Studied Nasal drug delivery was reliable and promising method for the systemic administration of specific molecules. The study provided detailed information regarding the anatomy of the nasal cavity and the mechanisms of drug absorption. Researchers explored various strategies and novel formulations to enhance absorption and extend drug duration in the cavity. highlighted the recent advancements and the diverse applications of these delivery systems in treating various diseases.
7. **Charu Saxena *et.al***, (2019) ^[26] : Focused on the essential aspects of nasal drug delivery, including the structure and function of the nasal cavity and the formulation considerations for nasal sprays. Understanding these factors helped in designing effective nasal formulations and evaluating their in-vitro characteristics, which were important for ensuring the quality, safety, and therapeutic effectiveness of nasal spray products. The intranasal drug delivery system was an important and convenient route for administering drugs for local, systemic, and central nervous system (CNS) effects.
8. **Zainab E. Jassim *et.al***, (2018) ^[27] : Studied The convenience of administration and improved patient compliance is important in the design of nasal drug delivery system. Different strategies have been applied to improve the intranasal absorption such as the use of mucoadhesive polymers, permeation enhancers, cosolvents, and the use of enzymatic inhibitors. Intranasal drug delivery was found much promising route for administration of peptides and protein drugs. This review sets out to discuss strategies to improve nasal drug delivery.
9. **Cherubino Di Lorenzo *et.al***, (2013) ^[28]: Highlighted that prolonged use of nasal decongestants such as Naphazoline can contribute to chronic headache, and clinicians should carefully inquire about nasal decongestant use in patients presenting with persistent headaches and reported a 34-year-old man with chronic headache initially attributed to chronic sinusitis and treated with excessive use of Naphazoline Nitrate nasal decongestant. Naphazoline may initially produce analgesic effects through activation of adrenergic and opioidergic systems.
10. **Parmar Harshad *et.al***, (2010) ^[29]: Studied Nasal drug administration has been used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. Drugs are cleared rapidly from the nasal cavity after intranasal administration, resulting in rapid systemic drug absorption.
11. **Am J Dis Child. *et.al***, (1948) ^[30]: Studied accidental poisoning with Naphazoline Hydrochloride, a topical imidazoline derivative widely used as a nasal and ocular decongestant, represents a significant clinical concern, particularly in paediatric populations. Due to its α -adrenergic agonist activity, systemic absorption following accidental ingestion or excessive intranasal use can lead to serious toxic manifestations. The clinical presentation, toxicological mechanisms, and outcomes associated with Naphazoline Hydrochloride poisoning.

3. Aim and objective:

Aim:

- To Formulate, Develop and Evaluation of Naphazoline Nasal Spray using Pharmaceutical Drugs.

Objective:

- To develop and formulate a stable and effective nasal spray containing naphazoline for intranasal administration.
- To achieve rapid relief from nasal congestion by delivering the drug directly to the nasal mucosa.
- To ensure proper drug distribution and absorption through the nasal cavity for a faster therapeutic effect.
- To evaluate the physicochemical properties of the formulation, including pH, viscosity, clarity, and drug content.
- To assess the spray characteristics such as spray pattern, droplet size, and uniformity of dose.
- To study the stability and safety of the nasal spray formulation to ensure its effectiveness during storage and use.

4. Plan of work:

Literature Review:

- Study Naphazoline Nasal Spray formulations and therapeutic uses of naphazoline as a nasal decongestant.

Selection of pharmaceutical ingredients:

- Selection of excipients used in Nasal Spray formulations such as preservatives, stabilizers, buffers, and viscosity enhancers.

Preservative: Methyl paraben Isotonicity agent: Sodium Chloride Buffer: Sodium Phosphate Solvent: PEG 400

Humectant: Glycerine Vehicle: Purified Water

Pre-formulation Studies:

- Pre-formulation helps determine drug properties before formulation.
- Studies include:
 - Organoleptic properties (colour, odour, appearance)
 - Solubility analysis
 - pH determination
 - Drug–excipient compatibility study
 - Stability of drug

Formulation of buffer:

- Preparation of phosphate buffer using Sodium Phosphate / Potassium Phosphate.

Formulation of Nasal spray:

- Preparation of nasal spray solution using selected excipients.
- Dissolution of active drug.
- Adjustment of pH and isotonicity.
- Filtration of solution.

Filling and Packaging:

- Fill prepared formulation into sterile nasal spray bottles.
- Use metered spray pump to deliver accurate dose.

Evaluation of Nasal Spray:

Evaluation of a nasal spray includes testing parameters such as pH, drug content, viscosity, sterility, Stability Testing, spray pattern, and droplet size to ensure the quality, safety, and effectiveness of the formulation.

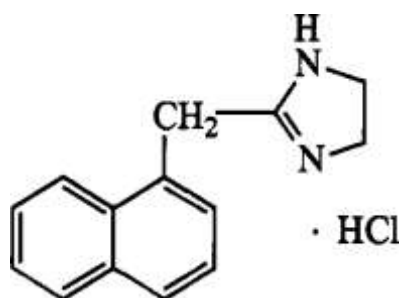
Result Analysis and Conclusion:

Interpretation of results and assessment of effectiveness.

5. DRUG AND POLYMER PROFILE

5.1 DRUG PROFILE:

- **Drug name:** Naphazoline.
- **Synonym:** Naphazoline hydrochloride.
- **Molecular formula:** C₁₄H₁₄N₂ * HCl.
- **Molecular Weight:** 246.74 g/mol. (31)
- **Structure:**



- **Category of Drug:** sympathomimetic vasoconstrictor.
- **IUPAC Name :** 2-[(naphthalen-1-yl)methyl]-4,5-dihydro-1H-imidazole hydrochloride.
- **Physical state:** White crystalline powder.
- **Melting point:** 155–260 °C. (32)
- **Solubility:** soluble in water and alcohol.
- **Pharmacodynamics:** Naphazoline (commonly used as Naphazoline hydrochloride) is a sympathomimetic α -adrenergic agonist used as a topical nasal decongestant.

Mechanism of action: Naphazoline is a vasoconstrictor that functions by stimulating alpha adrenergic

receptors in arterioles leading to decreased congestion at the site of administration. Naphazoline causes the release of norepinephrine in sympathetic nerves. Norepinephrine binds to alpha adrenergic receptors and causes vasoconstriction. Naphazoline is also a mild beta-adrenergic receptor agonist, which can cause rebound vasodilation after the alpha-adrenergic stimulation has ended. Naphazoline's release of norepinephrine also triggers a negative feedback loop which decreases production of norepinephrine, which can lead to rhinitis medicamentosa after long term use when naphazoline is stopped. (33)

Pharmacokinetics:

1. Absorption: Absorption data for naphazoline are scarce but imidazoline compounds in general are weakly basic and lipophilic, with high bioavailability from the gastrointestinal tract.

2. Volume of distribution:

Distribution data for naphazoline are scarce but imidazoline compounds are distributed throughout the body and can cross the blood-brain barrier.

3. Metabolism:

Metabolism data for naphazoline are scarce. Imidazoline compounds undergo some hepatic metabolism but a large fraction of the dose may be excreted unchanged in the urine.

4. Half-life:

Half-life has not been determined but effects last for 4 to 8 hours. Other imidazoline compounds have half-lives varying from 2 to 12 hours. (34)

Route of elimination

Imidazoline compounds undergo some hepatic metabolism but a large fraction of the dose may be excreted unchanged in the urine. Urinary excretion is higher with more acidic urine.

Uses of Naphazoline Nasal Spray

- i. Relief of nasal congestion (common cold)
- ii. Allergic rhinitis (hay fever)
- iii. Acute rhinitis
- iv. Sinusitis (adjunct therapy)
- v. Pre-procedural nasal decongestion. (35)

5.2 POLYMER PROFILE : (36-39)

5.2.1 SODIUM CMC : Sodium CMC is a semi-synthetic, water-soluble polymer derived from cellulose, where some hydroxyl (-OH) groups are substituted with carboxymethyl (-CH₂COO⁻Na⁺) groups.

Chemical Information

Chemical name: Sodium carboxymethyl cellulose Molecular formula: Variable (depends on substitution)

Polymer type: Anionic polysaccharide

Source:

Cellulose (plant origin) Structure :

Backbone: β -(1 \rightarrow 4) linked glucose units (same as cellulose) Substitution: – CH₂COONa groups replace –OH groups This substitution makes it water-soluble, unlike cellulose.

Physicochemical Properties :

- White to off-white powder
- Odourless, tasteless
- Highly water-soluble (forms colloidal solution)
- Forms viscous gel-like solution
- pH: ~6–8 (neutral to slightly alkaline)
- Hygroscopic (absorbs moisture)

Mechanism of Action (in formulations):

Hydrates in water \rightarrow swells \rightarrow forms viscous network Provides thickening and stabilization

Interacts with mucin \rightarrow gives mucoadhesion

Pharmaceutical Uses :

1. Viscosity Enhancer
2. Mucoadhesive Agent
3. Stabilizer
4. Controlled Release Agent

Role in Nasal Spray (Formulation)

- Increases viscosity of spray
- Enhances contact time with nasal mucosa
- Improves drug absorption
- Works synergistically with gellan gum.

Advantages :

- Non-toxic and biocompatible
- Non-irritant
- Easy availability
- Cost-effective
- Good stability over wide pH range

Limitations :

- High viscosity at high concentration (difficult to spray)
- Can support microbial growth \rightarrow needs preservative
- Sensitive to high salt concentration

Typical Concentration :

0.25% – 2% (depending on formulation)

Storage :

- Store in airtight container
- Protect from moisture

5.2.2 GELLAN GUM: Gellan gum is a natural, high molecular weight polysaccharide polymer produced by fermentation using the bacterium *Sphingomonas elodea*. It is widely used as an in-situ gelling agent in pharmaceutical formulations.

Chemical Information :

Type: Natural polymer (polysaccharide) Source: Microbial fermentation

Nature: Anionic polymer

Composition: Repeating tetrasaccharide units of: Glucose

Glucuronic acid Rhamnose

Structure : Linear polymer chain

Types of Gellan Gum :

High Acyl Gellan Gum

- Elastic gels
- Low Acyl Gellan Gum
- Brittle gels

Physicochemical Properties :

- Off-white powder
- Odourless and tasteless
- Soluble in hot water
- Forms clear gels
- Stable over wide pH range (3–10)
- Gelation temperature: ~30–40°C

Mechanism of Gel Formation

Gellan gum shows ion-activated in-situ gelation: Dissolves in solution (liquid form)

On contact with cations (Na^+ , Ca^{2+} in nasal fluid): Polymer chains align

Double helix formation

3D network structure forms.

Pharmaceutical Uses

- In-situ gelling agent
- Increases nasal residence time

- Provides sustained/controlled drug release
- Improves bioavailability
- Reduces nasal drainage and drug loss
- Enhances patient compliance
- Acts as viscosity enhancer
- Stabilizes formulation.

Role in Nasal Spray (Formulation)

- Forms gel when exposed to nasal ions
- Increases residence time in nasal cavity
- Reduces drug drainage

Advantages

- Biocompatible and non-toxic
- Requires low concentration (0.1–1%)
- Clear and elegant gels
- Ion-sensitive (ideal for in-situ systems)
- Good patient compliance

Limitations

- Requires presence of ions for gelation
- Can be brittle (low acyl type)
- Costlier than some polymers

Typical Concentration

0.1% – 0.5% (commonly used in nasal formulations)

Storage

- Store in dry, cool place
- Protect from moisture

5.2.3 POLYETHYLENE GLYCOL (PEG) :

Polyethylene Glycol (Peg) is a synthetic, hydrophilic polymer formed by polymerization of ethylene oxide. It is widely used in pharmaceuticals as a solvent, plasticizer, and stabilizing agent.

Chemical Information

Chemical name: Polyethylene glycol General formula: $H-(O-CH_2-CH_2)_n-OH$ Polymer type: Polyether

Nature: Non-ionic, hydrophilic Classification (Based on Molecular Weight) **Type**

- PEG 200–600
- PEG 1000–6000
- PEG >6000
- PEG 400

Physicochemical Properties :

- Colourless , odourless
- Hygroscopic (absorbs moisture)
- Completely water-soluble
- Miscible with many organic solvents
- Low toxicity
- Stable over wide pH range

Mechanism of Action (in formulations) : Dissolves both hydrophilic and some lipophilic drugs Reduces intermolecular forces → improves solubility

Forms hydrogen bonds with water → enhances stability

Pharmaceutical Uses :

1. Solvent / Co-solvent
2. Plasticizer
3. Humectant
4. Permeation Enhancer
5. Lubricant
6. Ointment / Suppository Base

Role in Nasal Spray :

- Enhances drug solubility (important for uniform dosing)
- Improves spreadability of formulation
- Reduces irritation of nasal mucosa
- Maintains moisture in nasal cavity
- Helps in uniform drug distribution

Advantages

- Non-toxic and biocompatible
- Good solubilizing capacity
- Chemically stable
- Compatible with many drugs
- Easy to handle

Limitations

- High concentration may cause irritation
- Can interact with some drugs (oxidation)
- Hygroscopic (absorbs moisture from air)

Typical Concentration

Usually 1% – 20% (depending on formulation)

Storage

- Store in tightly closed container
- Protect from moisture and heat

5.2.4 METHYL PARABEN :

Methyl paraben is a widely used antimicrobial preservative in pharmaceutical formulations. It belongs to the paraben group (esters of para-hydroxybenzoic acid) and is used to prevent microbial contamination.

Chemical Information

- Chemical name: Methyl p-hydroxybenzoate
- Molecular formula: $C_8H_8O_3$
- Class: Paraben (ester of p-hydroxybenzoic acid)
- Nature: Non-ionic compound

Physicochemical Properties

- White crystalline powder
- Odourless or faint odor
- Slightly soluble in water
- Freely soluble in alcohol
- Stable over wide pH range (4–8)
- Melting point: $\sim 125\text{--}128^\circ\text{C}$

Mechanism of Action

Inhibits growth of bacteria and fungi Disrupts microbial cell membrane

Interferes with enzyme activity → prevents microbial metabolism

Pharmaceutical Uses

1. Preservative
2. Antimicrobial Agent
3. Used in Various Dosage Forms
4. Nasal sprays
5. Syrups
6. Creams and lotions
7. Ophthalmic preparations

Role in Nasal Spray :

- Prevents microbial contamination during storage and use
- Ensures safety of formulation
- Maintains product stability and shelf life
- Advantages

- Effective at low concentration
- Stable and compatible with many excipients
- Non-irritant at recommended levels
- Cost-effective

Limitations

- Less effective against Gram-negative bacteria
- May require combination with other preservatives (e.g., propyl paraben)
- Rare cases of hypersensitivity

Typical Concentration

0.1% – 0.25%

Storage

- Store in well-closed container
- Protect from light and moisture

5.2.5 GLYCERINE:

Glycerine is a clear, colourless, viscous liquid belonging to the polyol (trihydric alcohol) group. It is widely used in pharmaceutical formulations as a humectant, solvent, and plasticizer.

Chemical Information

Chemical name: Glycerol / Propane-1,2,3-triol Molecular formula: $C_3H_8O_3$

Class: Polyol (trihydric alcohol) Nature: Hydrophilic

Structure

Contains 3 hydroxyl ($-OH$) groups

Physicochemical Properties

Colourless, odourless, sweet-tasting liquid Highly viscous

Completely miscible with water and alcohol Hygroscopic (absorbs moisture from air) Boiling point: $\sim 290^\circ C$

Stable and non-volatile

Mechanism of Action

Attracts and retains water due to $-OH$ groups Forms hydrogen bonds with water molecules Keeps formulation hydrated and prevents drying **Pharmaceutical Uses**

1. Humectant
2. Solvent / Co-solvent.
3. Plasticizer
4. Sweetening Agent
5. Viscosity Enhancer
6. Lubricant

Role in Nasal Spray

- Maintains moisture of nasal mucosa
- Prevents irritation and dryness
- Improves patient comfort
- Enhances smooth flow of spray

Advantages

- Non-toxic and safe
- Biocompatible
- Sweet taste (useful in oral formulations)
- Excellent moisture-retaining property
- Widely available and economical

Limitations

- High concentration may cause irritation
- Sticky nature at high viscosity
- Hygroscopic (absorbs moisture from air)

Typical Concentration

Usually 5% – 20% (depending on formulation)

Storage

- Store in tightly closed container
- Protect from moisture

5.2.6 SODIUM CHLORIDE:

(NaCl) is an inorganic electrolyte widely used in pharmaceutical formulations to maintain tonicity and ionic balance.

Chemical Information Chemical name: Sodium chloride Molecular formula: NaCl

Class: Inorganic salt / electrolyte

Nature: Ionic compound (Na^+ and Cl^- ions) Structure :Composed of:

Sodium ion (Na^+) Chloride ion (Cl^-)

Arranged in a crystalline lattice structure

Physicochemical Properties

- White crystalline powder
- Odourless, saline taste
- Freely soluble in water
- Stable and non-hygroscopic
- pH: Neutral (7)

Mechanism of Action (in formulations) Dissociates into Na^+ and Cl^- ions in water Maintains osmotic balance (tonicity)

Provides ions that can activate certain polymers (like gellan gum)

Pharmaceutical Uses

1. Tonicity Adjusting Agent
2. Electrolyte Source
3. Gel Activator
4. Stabilizer
5. Diluent / Vehicle Modifier

Role in Nasal Spray

- Adjusts tonicity to match nasal fluid (~0.9% NaCl)
- Prevents:
 - Nasal irritation
 - Tissue damage
- Helps gellan gum to form gel
- Improves patient comfort

Advantages

- Safe and non-toxic at required concentration
- Easily available and economical
- Compatible with most formulations
- Essential for isotonicity

Limitations

- High concentration → irritation
- May affect viscosity of some polymers
- Excess ions may destabilize formulation

Typical Concentration 0.9% w/v (isotonic solution) **Storage**

- Store in well-closed container
- Protect from moisture

6. EXPERIMENTAL WORK:

➤ **Material used:**

- Naphazoline HCl
- Sodium CMC
- Gellan gum
- PEG 400
- Glycerine
- Methyl paraben
- Sodium chloride
- Purified water

➤ **Instruments used:**

- Digital pH Meter
- Ostwald Viscometer
- UV-Visible Spectrophotometer
- Burner
- Beaker
- Density bottle
- Conical flask
- Round bottle flask
- Franz cell apparatus.

➤ **Table-2: Different batches of Nasal spray formulation:**

Ingredients	F1	F2	F3	F4	F5	F6
Naphazoline HCl	5mg	5mg	5mg	5mg	5mg	5mg
Sodium CMC	0.01ml	0.01ml	0.01ml	0.01ml	0.01ml	0.01ml
Gellan gum	0.2gm	0.15gm	0.12gm	0.1gm	0.7gm	0.05gm
PEG 400	1.5ml	1.5ml	1.5ml	1.5ml	1.5ml	1.5ml
Glycerine	0.25ml	0.25ml	0.25ml	0.25ml	0.25ml	0.25ml
Methyl paraben	0.003gm	0.003gm	0.003gm	0.003gm	0.003gm	0.003gm
Sodium chloride	0.27	0.27	0.27	0.27	0.27	0.27
Purified water	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml

The developed spray formulation was evaluated using various physicochemical and performance parameters. These evaluation tests are essential to ensure the quality, stability, uniformity, and reproducibility of the formulation. Each parameter provides important information regarding the behavior of the spray during storage and administration.

6.1 THE EVOLUTION TEST PROCEDURE (F1-F6)

The prepared nasal spray formulations were evaluated for physicochemical parameters such as appearance, pH, density, viscosity, spray pattern, volume per spray, percentage of drug release. These tests were performed to determine the quality, stability, and suitability of the formulation for nasal application and to select the optimized batch.

6.2 APPEARANCE & CLARITY

The formulated solutions were evaluated as in-house test for appearance (colour) as well as their clarity. The colour and clarity were visually examined against black and white surface in inspection.

Method:

The formulation was observed against both light and dark backgrounds to assess the following characteristics:

- Clarity
- Colour
- Presence of particulate matter
- Homogeneity.

6.3 pH Measurement

The pH of the spray formulation was determined using a calibrated digital pH meter. Method:

- The pH meter was calibrated using standard buffer solutions (pH 4.0 and pH 7.0).
- The electrode was rinsed with distilled water before measurement.
- The pH of the formulation was recorded. (36)

6.4 Spray Pattern

The characterization of spray is the pathway through which the performance of the pump and the nozzle of container closure system need to be evaluated. In the evaluation of the spray pattern, the spray distance between the nose- piece and the collection surface, orientation of the nose-piece, and visualization procedure are specified. Spray Pattern of prepared nasal spray formulation was measured by the Spray view system. The parameters of spray pattern assessment are height at 5cm, evacuation time 15 second. Sprays were tested in both vertical and horizontal orientations.

Measurements:

D_{max} – Maximum diameter of spray pattern
 D_{min} – Minimum diameter of spray pattern
Diameter Ratio = D_{max} / D_{min} . (37)

6.5. Density measurement

Density is a measure of how much mass is contained in a given volume of a substance. In simple words, it tells us how “compact” or “crowded” the particles are.

- Formula: Density= mass / volume
- SI Unit: kg/m³ (kilogram per cubic meter) / unit: g/cm³

- Method to Calculate Density:

Measure the mass (m): Use a balance to find the mass of the object.

Measure the volume (V): For regular objects → use formula (like length × breadth × height) For irregular objects → use water displacement method

Apply the formula: Divide mass by volume.(38)

6.6 Viscosity measurement

Viscosity of the spray solution was determined using an Ostwald viscometer. Method:

- The formulation was filled into the viscometer.
- Flow time between two fixed points was recorded.
- Measurements were repeated three times.
- Temperature was maintained constant.(39)

6.7. Volume per spray

Volume per spray determines the consistency of dose delivery. Method:

- The container was weighed before spraying (W_o).
- The container was weighed after spraying (W_t). Calculation: $V_s = (W_o - W_t) / \rho$

Where: V_s = Volume per spray, W_o = Initial weight W_t = Final weight, ρ = Density of formula

This parameter ensures dose accuracy, reproducibility, and uniform drug delivery.

6.8 Percentage of drug release

Percentage of Drug Release is a common calculation in pharmaceuticals (especially in dissolution studies) to determine how much of a drug has been released from a dosage form over time.

Formula: percentage Drug release = (Amount of drug released/Total amount of drug) x 100
Amount of drug released = quantity of drug dissolved at a specific time.

Total amount of drug = initial amount of drug present in the dosage form.

The above evaluation parameters are essential for assessing the physicochemical characteristics, spray performance, dose uniformity, and overall quality of the spray formulation. These tests collectively ensure that the formulation meets pharmaceutical standards for stability, reproducibility, and patient acceptability.

(40)

7. Results:

7.1 General Observation of Formulations (F1-F6)

All formulations showed acceptable physicochemical properties suitable for to nasal application and No phase separation or instability was observed, indicating good formulation design.

According to IP, nasal spray formulations should be clear, homogeneous, and free from particulate matter and phase separation. All prepared nasal spray formulations satisfied these requirements, indicating good formulation design and stability suitable for nasal administration.

7.2 Appearance & Clarity:

All batches showed clear and colourless solution with no visible particulate matter.

According to IP, formulation should be clear and free from turbidity; all formulation complied with this

standard.

7.3 pH Measurement:

The pH values of all batches were within the range of 6 to 6.5, which is suitable for nasal application. The pH values of all formulations were found. The F1 formulation had a pH of 6.3, F2 formulation showed a pH of 6, while F3 formulation had a pH of 6.4. The F4 formulation showed a pH of 6.2. F5 formulation showed a pH of 6.5, and The F6 formulation showed a pH of 6.5. These pH values are suitable nasal spray formulations.

According to IP, acceptable pH range for nasal spray preparation is 4.5-6.5; the observed values were within the prescribed limits.

7.4 Spray Pattern:

The spray pattern differed depending on the formulation composition. The F1, F5, F6 formulation produced a circular spray pattern, which is generally considered uniform and effective for nasal sprays. The F2 and F4 formulations produced an oblong spray pattern, while the F3 formulation showed an irregular spray pattern, indicating less uniform dispersion, as found according to IP.

7.5 Density Measurement:

The density the formulations. The F1 formulation density of 1.12g/ml, while F2 are 1.08g/ml. The F3 formulation are 1.03g/ml, F4 formulation are 1.03g/ml, and the F5 formulation density is 1.01g/ml, the F6 formulation showed density are 1.04g/ml.

According to IP, density of nasal spray should be 1.0 g/ml; the observed values were within the prescribed limits.

7.6 Viscosity Measurement:

The viscosity values ranged between 3.23 and 4.4 cp. F1 showed the viscosity 4.4cp because large amount of Gellan gum compare to others. The F2 formulation had viscosity 4.05cp. The F4 formulation showed viscosity 3.5cp, the F5 viscosity 3.3cp, and. F1 showed the viscosity 3.23cp.

According to IP, viscosity of nasal spray should be 1 to 20cps; the observed values were within the prescribed limits.

7.7 Volume Per Spray:

The volume delivered in each spray ranged from 0.9 ml to 1.2 ml. The F6 formulation de-livered (1.2 ml) per spray, while F5 delivered 1.1 ml. The F4 formulation produced 1.1ml per spray. The F3 formulation had the spray volume (1ml), The F2 formulation produced 0.9ml, and The F1 formulation de-livered (0.9 ml) per spray, as found according to IP.

7.8 Percentage of Drug Release: Table-3

time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	36.5	38.12	47.45	50.89	56.79	84.3
10	41.49	45.92	53.75	57.37	65.52	99.81
15	50.77	52.54	58.29	64.04	79.46	
20	58.52	60.86	73.73	73.36	93.95	
25	64.58	68	79	80.55		
30	71.3	77.81	87.81	93.34		
35	78.71	84.53	99.34			
40	86.83	96.34				
45	93.23					
50	97.82					

Graph:

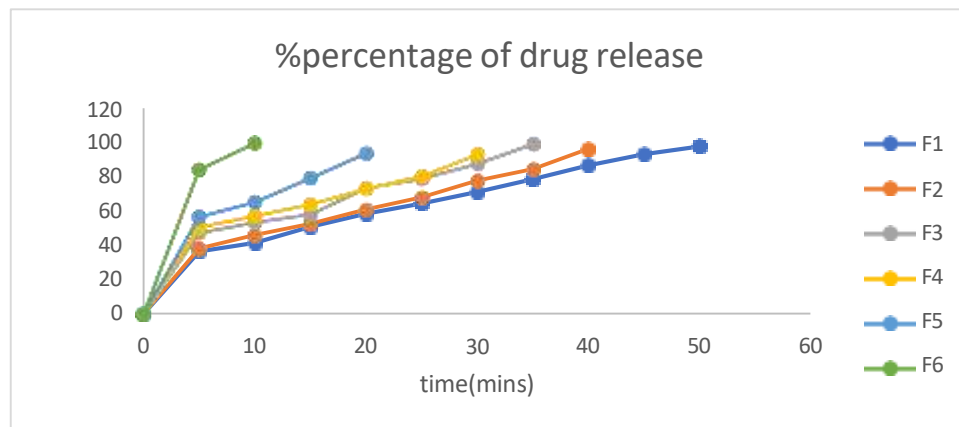


Fig 5. % percentage of drug release.

➤ **Table-4: TABULAR RESULT OF ALL EVALUATION TEST**

PARAMETERS	F1	F2	F3	F4	F5	F6
APPREANCE (COLOUR)	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Clear Solution
pH	6.3	6	6.4	6.2	6.5	6.5
Spray Pattern	Circular	oblong	irregular	oblong	Circular	Circular

Density Measurement (g/ml)	1.12	1.08	1.03	1.03	1.01	1.04
Viscosity (cps)	4.4	4.05	3.5	3.5	3.3	3.23
Volume of each spray (ml)	0.9	0.9	1	1.1	1.1	1.2
Percentage of drug release(min)	50	40	35	30	20	10

8. Summary and Conclusion :

All evaluation parameters of the Naphazoline Nasal Spray formulations (F1–F6), it can be concluded that all formulations showed clear appearance, indicating good compatibility of ingredients. The pH range (6.0–6.5) was found to be suitable for nasal administration, ensuring minimal irritation to the nasal mucosa.

The spray pattern study revealed that F1, F5, and F6 produced a uniform circular pattern, which is desirable for effective drug distribution, whereas F3 showed an irregular pattern. The density and viscosity values were within acceptable limits for nasal sprays. A gradual decrease in viscosity from F1 to F6 was observed, which contributed to better spray ability and drug release. The volume per spray was consistent across formulations, with F5 and F6 showing slightly higher values, ensuring adequate dose delivery. The drug release study indicated that F6 showed faster drug release, while F1 showed the slowest release due to higher viscosity.

Overall, formulation F6 can be considered optimized, as it provides: Suitable pH good spray pattern (circular), Acceptable viscosity and density and better drug release profile.

Thus, F6 is the most promising formulation for effective nasal drug delivery of naphazoline.

9. FUTURE SCOPE:

○ Clinical Testing on Patients

Test the nasal spray on patients with congestion or allergic rhinitis to confirm its safety and effectiveness in clearing nasal passages.

○ Stability Testing

Check how long the spray remains safe and effective under different storage conditions (heat, humidity, room temperature), specifically monitoring for changes in viscosity or pH.

○ Microbial Testing

Test the spray against common bacteria and viruses found in the nasal cavity to prove its antimicrobial and antiviral action.

- Safety Studies

Conduct toxicity and mucosal irritation studies to ensure the spray is completely safe for regular use on sensitive nasal membranes.

- Use of Natural Preservatives

Replace synthetic preservatives with natural alternatives to make the formulation fully herbal and non-irritating.

- Long-Term Use Study

Study the effects of repeated use to confirm there is no "rebound effect" (worsening congestion after stopping) or damage to the nasal cilia.

- Large-Scale Production

Develop methods for manufacturing the spray on a commercial scale while maintaining sterile conditions.

- Packaging Improvement

Improve the pump design for a finer mist, better dose control, and an ergonomic nozzle for easy nasal insertion.

- Application for Other Conditions

Study its use for sinusitis, nasal polyps, dryness caused by air travel, and post-surgical nasal care.

- Special Formulations

Develop "Extra Strength" versions for severe congestion or "Ultra Gentle" versions specifically for infants and toddlers.

10. References :

1. Chien Y, "Novel Drug Delivery System", Drugs and Pharmaceutical Sciences, Revised and Expanded, 2024, 2(5)229.
2. Payal Ramesh Gaikwad, Sanjana Shridhar Walwante, Nandkishor Deshmukh, Dr. Swati Deshmukh, "Excipients Used In Nasal Spray Formulation", Indo American Journal of Pharmaceuticals Sciences, 2025, 12(01), 249-256.
3. Santosh Thorat, "Formulation and Product Development of Nasal Spray", Scholars Journal of Applied Medical Sciences, 2016, 4(8D), 2976-2985.
4. Mr. Nilesh Bhaskar Khairnar, Ms. Rajeshwari K. Thokal, Dr. Gajanan S. Sanap, Nasal Spray, "Sanap, Nasal Spray," International Journal of Research Publication and Reviews, 2023, 4(3), 4779-4788
5. Kant A, Reddy S, Shankraiah M, Venkatesh J, In situ Gelling System, Pharmacology online, 2011, 2(6) 28-44.
6. Aubrey Bailey, "How to Tell if You Have Nasal Polyps," Physical Therapist, Doctor of Physical Therapy, Certified Hand Therapist, 2024, (05), 176.
7. Lin Lin ORCID and Lei Cheng, "Current and Emerging Treatment Options in Sinus and Nasal -8-8 Diseases; A Promising Future in the Appropriate Therapies," Journal Clinical Medicine 2022, 11 (24), 73-98.
8. Lindsay Curtis, "Signs and Symptoms of a Deviated Septum", 2024, 22, (01), 10-20.

9. Shirwa Sheik-Ali, Sharaf Sheik, “ Vestibular furunculosis: Summarised case series,” World Journal of Otorhinolarygology, 2022, (08), 2- 21.
10. Sabale Anjalia, Kulkarni Abhijeet, Sabale Ajay, “Nasal In Situ Gel: Novel Approach for Nasal Drug Delivery”, Journal of Drug Delivery and Therapeutics, 2020; 10(2)183-197.
11. Putheti R., Patil M. C., Obire O.; Nasal Drug delivery in Pharmaceutical and biotechnology: present and future; e-Journal of Science & Technology; 2009; (3), 1-19.
12. Graff L.C., Pollock G.M. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci. 2005; 94:1187-1195.
13. Romeo V. D, Meireles J, Sileno A. P., Pimplaskar H. K., Behl C. R. Effects of physicochemical properties and other factors on systemic nasal delivery; Adv Drug Deliv Rev, 1998; 29: 89-116.
14. Prasad K. More, Ravindranath B. Saudagar, and Sheetal B Gondkar, “ Nasal In situ Gel A Novel approach For Nasal Drug Delivery System,” World Journal Of Pharmaceutical Research,2014,4(2),686-708.
15. Pagar S. A., Shinkar D., Saudagar R.; A Review on Intranasal Drug Delivery System; J. Adv. Pharm. Edu. & Res.; Oct-Dec 2013; 3 (4), 333-346.
16. Singh kumar Arun.Nasal cavity: A promising transmucosal platform for drug delivery and research approach from nasal to brain targeting. Journal of Drug Delivery and Therapeutics. 2012,2(3)22-33.
17. Chajed S., Sangle S., and Barhate S. Advantagious nasal drug delivery system; A review. International journal of pharmaceutical science and research.2011; 2(6),1322-1336.
18. Zaheer A., Sachin., Swamy. Mucoadhesive Polymers: Drug Carriers for Improved Nasal Drug Delivery.Indian Journal of Novel Drug Delivery. Jan-Mar,2012; 4(1), 2-16.
19. Dhuria SV, Hanson LR, Frey WH II. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. Journal of Pharmaceutical Sciences, 2010; 99(4),1654–1673.
20. Lohare Rahul Sanjay, a Makka Krupali Ashokbhai,a Shubham Ghatole,a Subhadeep Roy, Kardile Punam Kashinatha and Santanu Kaity, “Strategies for beating the bitter taste of pharmaceutical formulations towards better therapeutic outcomes” RSC Pharm., 2025, 2, 59–81.
21. Shuhua Wei , Zizhao Zhai , Xi Kong , Chuanbin Wu a, Bing Zhu ,Ziyu Zhao, Xuejuan Zhang, “drug delivery system: The strategies to enhance the efficiency of intranasal drug delivery by improving drug absorption,”2025,676.
22. Letícia Apolinário Carlos da Silva ,Mirella Camargo do Nascimento ,Thaís Ranielle Souza de Oliveira, “ Assessing risks and adverse effects of naphazoline hydrochloride: a literature review”, Scientific Electronic Archives, 17 (2), 2024.
23. Nehad Jaser Ahmed and Hasan Soliman Yusufoglu, “The Use of Ophthalmic and Nasal Naphazoline in the Outpati. ent Setting”, Journal of Pharmaceutical Research International, 2021,19-23,2231-2919.
24. Mirajkar Reshma Nilesh , Devkar Mangesh Shivaji, “Taste masking methods and agents in pharmaceuticals formulation” International research journal of pharmacy,2021,3(8)66-89.
25. Sulaiman Alnasser, “A Review On Nasal Drug Delivery System And Its Contribution In Therapeutic

Management”, Asian Journal Pharmaceutical Clinical Research ,12, (1),2019, 40-45.

26. Charu Saxena, Kunal Arora, Lovely Chaurasia, “Importance of Different Novel Nasal Drug Delivery System-A Review”. International Journal of Pharmaceutical and Clinical Research 2019; 11(1)13-19.
27. Zainab E. Jassim, Entidhar J. Al-Akkam , “A review on strategies for improving nasal drug delivery systems”, Drug Invention Today, 2018,10(1) 11-23.
28. Cherubino Di Lorenzo , Gianluca Coppola , Valeria La Salvia , Francesco Pierelli, “Nasal decongestant and chronic headache: a case of naphazoline overuse headache? S
29. Parmar Harshad, “Recent Techniques In Nasal Drug Delivery: A Review, International Journal of Drug Development & Research,2010,2 (3)55-76.
30. Parmar Harshad, “Recent Techniques In Nasal Drug Delivery: A Review, International Journal of Drug Development & Research,2010,2 (3)55-76.
31. Allen, L. V., Popovich, N. G., & Ansel, H. C.Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott Williams & Wilkins, 2014,4(5),54-67.
32. Kalkotwar, R. S., Bankar Patil, V. V., Patel, A. M., “Evaluation and Quality Control of Nasal Spray”Journal of Drug Delivery and Therapeutics,2016,9(5),334-445.
33. Vardanyan, R. S., & Hruby, V. J. “Synthesis of Essential Drugs. Elsevier Academic Press – chapter on Naphazoline” 2018,12(1) 71-83.
34. Aulton, M. E., & Taylor, K. Aulton’s Pharmaceutics: The Design and Manufacture of Medicines. Elsevier, 2018,2(3)88.
35. Paul H. Ratner MD, MBA Paul M. Ehrlich MD Stanley M. Fineman MD, MBA Eli O., Meltzer MD d, David P. Skoner MD, “Use of Intranasal Cromolyn Sodium for Allergic Rhinitis Author links open overlay panel,” Mayo Clinic Proceeding, 2002, 77, (4), 350-354.
36. Patrick J. Sinko, Yashveer Singh, “Martin's Physical Pharmacy and Pharmaceutical Sciences” ,Lippincott Williams & Wilkins,2011,6(2)450-560.
37. Rowe RC, Sheskey PJ, Quinn ME “Handbook of Pharmaceutical Excipients”.London: Pharmaceutical Press; 2009,6,656-678.
38. Hillery AM, Lloyd AW, Swarbrick J. “Drug Delivery and Targeting for Pharmacists and Pharmaceutical Scientists”,London: Taylor & Francis; 2001,7(8)88-99.
39. Ansel HC, Popovich NG, Allen LV “Jr. Pharmaceutical Dosage Forms and Drug Delivery Systems” Philadelphia: Lippincott Williams & Wilkins; 2011,9(6)5567-7654.
40. Patil Vidya Bankar, Kalkotwar RS, Patel Ankita, Tathe Swati , Jadhav VB , “Evaluation And Quality Control of Nasal Spray,” Journal of Drug Delivery & Therapeutics; 2012, 2(4), 1-4.
41. Aida Maaz, Ian S. Blagbrough and Paul A. De Bank, “Review In Vitro Evaluation of Nasal Aerosol Depositions,” An Insight for Direct Nose to Brain Drug Delivery Pharmaceutics 2021, 13, 1079
42. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy CBS Publishers; 2013,8(5),79.

43. 39.Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. Wolters Kluwer; 2016.8(6)57-89.
44. Falgun Bhuvra, L D Patel, Krutagn Patel, "Factorial Design Methodology for Development of Pediatric Nasal Spray: Study on Xylometazoline Nasal Solution Used For Treatment of Nasal Congestion,2013,8(4)556-677.

Copyright & License:

© Authors retain the copyright of this article. This work is published under the Creative Commons Attribution 4.0 International License (CC BY 4.0), permitting unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.