

FORMULATION & EVALUATION OF NASAL SPRAY FOR TREATMENT AND MANAGEMENT OF ACUTE MIGRAINE

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ABSTRACT

Acute migraine is a frequent neurological disease consisting of moderate to severe headache, and often nausea, vomiting, photophobia and phonophobia. During migraine attack, oral dosage may be difficult so there is a need for convenient and fast acting non-oral dosage forms. The present study focused on formulation of Sumatriptan succinate nasal spray for the treatment and assessment of acute migraine, which was a condition of the day. Sumatriptan succinate, a selective 5-HT_{1B}/5-HT_{1D} receptor agonist, was selected because it has been shown to be effective in the treatment of acute migraine and because it is administered intranasally. Preformulation studies performed in the formulation-development approach comprised physical characterization, solubility testing, determination of the analytical wavelength and drug-excipient compatibility testing. Nasal spray formulations were prepared in proper aqueous vehicles with the aid of buffering agents, tonicity adjusting agents and (if required) viscosity and/or permeation modifying excipients. The appearance, clarity, pH, viscosity, drug content, in-vitro drug release, uniformity of delivered-dose, spray pattern, droplet-size distribution, osmolality, stability and microbiological quality and nasal tolerability of the prepared formulations were evaluated. Optimization was done as a function of the critical formulation and spray-performance parameters. The intranasal system is non-invasive, easy to use and may be particularly beneficial in patients who are unable to swallow a tablet due to nausea or vomiting. Overall, Sumatriptan succinate nasal spray is a potentially good dosage form for acute migraine treatment, but this must be adequately substantiated in the clinical efficacy in the developed form via experiments and trials.

Keywords: Sumatriptan succinate; Nasal spray; acute migraine; intranasal drug delivery; Formulation and evaluation.

INTRODUCTION

Migraine is one of the most common neurological disorders, is a recurring, moderate to severe headache. May cause nausea, vomiting and hyperacusis (sensitivity to light and sounds). Acute migraine attacks can interfere with your daily life, employment, education and quality of life. So, treatment needs to be both quick and effective to help control migraine symptoms. Oral medication is often used to relieve migraine and may be delayed – it has to pass through the stomach and intestine before getting to the blood supply. With nausea and vomiting, it may be difficult to swallow food.

Intranasal is an important alternative to treatment of acute migraine. A nasal spray is used to spray a drug into the nose, allowing it to be absorbed through the lining of the nose. This route may be speedier acting and may be useful in patients that experience nausea or a trouble with swallowing tablets. Moreover, nasal administration is convenient, non-invasive and easy-to-use. The formulation, however, should have desirable qualities such as suitable pH, proper drug content, viscosity, spray characteristics and stability^[1].

Sumatriptan succinate is chosen as a model drug for the present formulation. Sumatriptan is a selective serotonin receptor 5-HT_{1B}/5-HT_{1D} agonist for the acute treatment of migraine attack. It works primarily by contracting some of the blood vessels in the head, and inhibiting the release of chemicals that play a role in migraine pain. Sumatriptan is available in different formulations including tablets to take orally and a nasal spray. The nasal administration is especially beneficial when a quick therapeutic response is needed^[2].

The study develop and test a new nasal spray formulation of sumatriptan succinate for the treatment of acute migraine and to find the optimum dosage of the active ingredient. The formulation will be formulated by using appropriate pharmaceutical excipients for appropriate uniformity of drug delivery and good nasal performance. The prepared nasal spray can be tested for various parameters including appearance, pH, drug content, viscosity, spray pattern, delivered dose, droplet or particle characteristics, and stability. The tests are used to evaluate the quality, safety, uniformity and performance of the formulation^[3].

Thus, the development of a nasal spray of sumatriptan succinate may provide an alternative (and perhaps more rapid) route of administration during an acute migraine attack. The main idea of the study is to develop a suitable drug formulation for delivering the drug into nose and provide the effective treatment for the acute migraine symptoms^[4].

AIM AND OBJECTIVES

Aim

To formulate, optimize and evaluate a sumatriptan succinate nasal spray as a suitable, stable and effective dosage form for the treatment and management of acute migraine.

Objectives

- To formulate a nasal spray containing sumatriptan succinate using suitable pharmaceutical excipients and an appropriate nasal delivery system.

- To optimize and evaluate the developed formulation for appearance, pH, viscosity, drug content, delivered-dose uniformity, spray pattern, droplet-size distribution, drug release and stability.
- To assess the therapeutic potential of the developed nasal spray as a convenient and potentially rapid approach for managing acute migraine, particularly when oral administration is difficult.

RESEARCH METHODOLOGY

The study was designed as an experimental formulation-development study for preparing and evaluating sumatriptan succinate nasal spray. Sumatriptan succinate was selected as the active pharmaceutical ingredient as it is proven to be effective in treating acute migraine attack and suitable for intranasal administration. Preformulation studies involved physical appearance, solubility studies, melting point determination, FTIR/DSC drug-excipient compatibility and determination of proper analytical wavelength. Purified water and appropriate buffering agents, sodium chloride and, if necessary, the viscosity and/or permeation modifying agents were used to prepare various formulations. The drug and excipients were accurately weighed and then dissolved and mixed under controlled conditions and adjusted for pH and volume and passed through appropriate filtration. The ready formulations were poured in appropriate metered nasal sprays. The appearance, clarity, pH, viscosity, drug content, in-vitro drug release, delivered-dose uniformity, spray pattern, droplet-size distribution, osmolality, stability, microbiological quality and nasal tolerability were evaluated for experimental batches. The selected optimized formulation was the one that had the best overall performance and formulation quality.

Acute Migraine: Pathophysiology, Symptoms and Current Treatment Approaches

Acute Migraine

Acute migraine is a moderate to severe headache that lasts several hours and sometimes several days, and is a neurological condition. It may be on one or both sides of the head. At the time of an attack, normal activities like walking around, climbing stairs or working can make the pain worse. Migraine can also be accompanied by nausea, vomiting, light sensitivity and sound sensitivity. In some people the aura may occur before or with the headache. Temporary visual changes, tingling, numbness or problems with speech may occur with Aura^[5].

Acute migraine attacks can be painful and have associated symptoms which can make it difficult for the person to do their normal everyday activities, therefore it is important that they are treated. Treatment is typically directed towards relieving the headache and symptoms of the headache. Simple analgesics, anti-inflammatory or non-steroidal medicines (NSAIDs), anti-emetics and some anti-migraine medicines (triptans) are medicines that may be used in medicines. Triptans are a group of drugs commonly used for acute migraine, one of which is sumatriptan. If the medicine is difficult to swallow because you are nauseated or vomit, nasal medicine might be useful. Sumatriptan comes in an intranasal (nasal) form that can be used to treat migraine headache and its symptoms^[6].

Pathophysiology

The exact mechanism of migraine is not known, and involves the interactions between the nerves, blood vessels and chemicals within the brain. In migraine headache, the trigeminovascular system may be a key component in the process of migraine pain. During a migraine attack the nerves in the trigeminal system are stimulated, which innervate the meninges and blood vessels of the brain. These nerves have the ability to release chemicals, such as calcitonin gene related peptide (CGRP). CGRP may cause blood vessels to become dilated and make the nerves sensitive to feelings of pain. This act helps to develop and maintain migraine pain^[7].

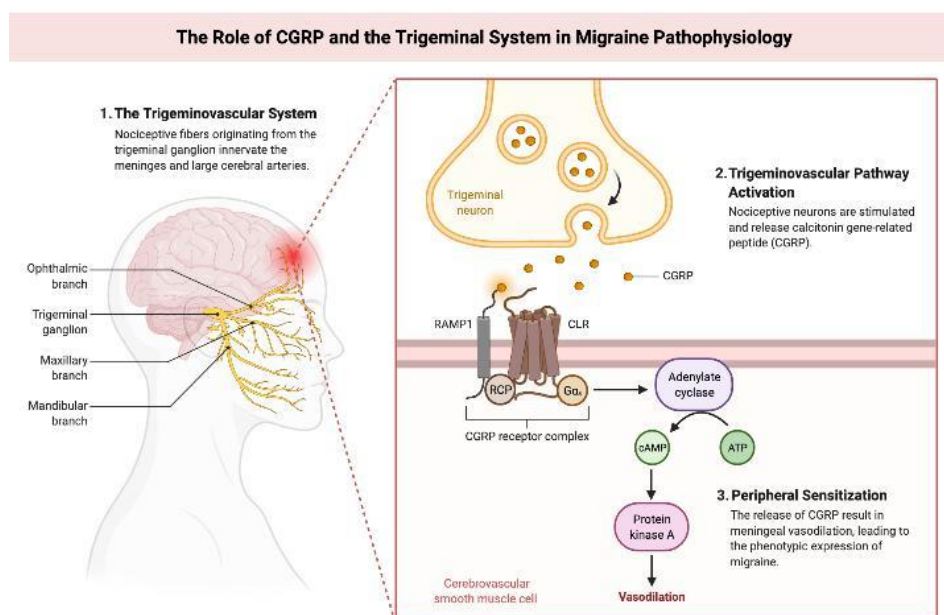


Image- 1: The Role of CGRP and the Trigeminal System in Migraine Pathophysiology

Sources: <https://sl1nk.com/6wyxozt>

The other process is termed cortical spreading depression (CSD): It is a wave of electrical activity across the cortex that takes place. CSD is related to migraine aura and is thought to activate trigeminal pathways. These pathways can result in an increase in the production of CGRP and other inflammatory factors. It can result in increased sensitivity of the nervous system (sensitisation)^[8].

Serotonin also plays a role in the actions of migraine disorder. That's why some medicines are referred to as "triptans". Sumatriptan is predominantly a 5-HT_{1B} and 5-HT_{1D} receptor agonist which has a beneficial effect on the reduction of migraine related activity. In this regard, trigeminal and serotonin pathways is a critical part of acute treatment of migraine^[8].

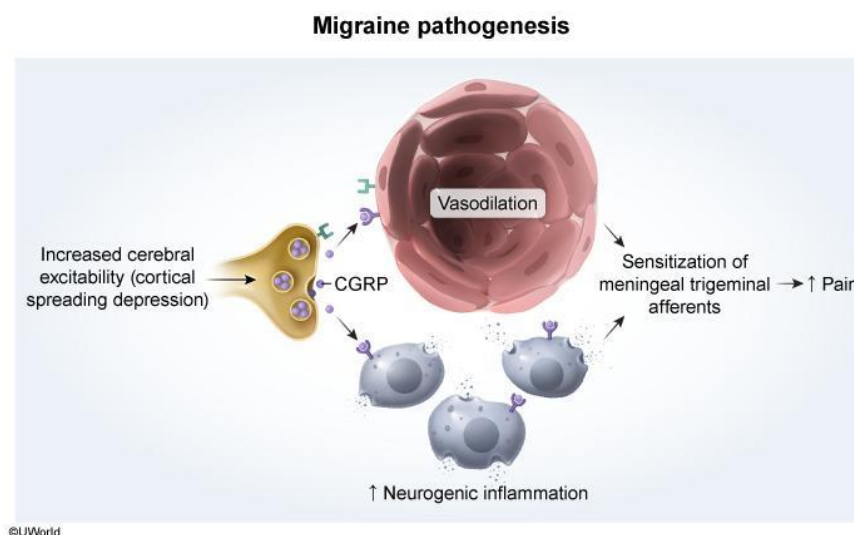


Image- 2: Migraine Pathogenesis

Sources: <https://sl1nk.com/6iinfib>

Symptoms and Current Treatment Approaches

- **Headache and Pain** - is the most important symptom of an acute migraine attack. It is typically a throbbing or pulsating pain, and can be on one side. The pain can get worse with exercise. The headache can last for several hours and start to affect one's normal work or activities.
- **Nausea, Vomiting and Sensitivity** - Many people experience sensitivity (tenderness) and nausea and vomiting as part of a Migraine. Some patients also may be very sensitive to light and sound. These symptoms may cause normal environments to be uncomfortable. Some people may have nausea and/or vomiting and may not be able to swallow pills or capsules as easily as they should be able to, therefore, it may be easier for them to take non-oral medications such as nasal sprays.
- **Simple analgesics and NSAIDs** – Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) can help treat mild or moderate acute migraine. Appropriate non-steroidal anti-inflammatory drugs (NSAIDs) can help relieve headache pain. Generally, treatment should commence early during the attack. Drugs will be chosen according to severity of the headache, history of response to drugs, symptoms and individual considerations.
- **Triptans and Sumatriptan**-Triptans are a class of drugs that can be used for acute moderate or severe migraine attacks. Sumatriptan is one of the most frequently used factor triptans, which act by binding to serotonin receptors that are linked to migraines. It comes in various forms of dosage such as a nasal spray. Sumatriptan is effective when administered nasally (up the nose) for the treatment of migraine headache and its associated symptoms.
- **Other Non-Oral Approaches** - For patients who can't swallow tablets, or if they are feeling sick, they may be able to benefit from nasal sprays. Sumatriptan is a nasal spray that is used right away in adults to treat a migraine attack. Medications can be given in other ways other than by mouth: subcutaneous medicines. The appropriate dosage form is to be based on the severity and nature of the migraine attack^[9].

Sumatriptan Succinate: Pharmacology, Mechanism of Action and Therapeutic Potential

Sumatriptan Succinate

Sumatriptan succinate belongs to a group of drugs known as triptans that block the spread of the migraine pain and are selective against migraine. It is mainly used for the acute treatment of migraine attacks, with or without aura, in adults. The active substance is sumatriptan, the salt form used for pharmaceutical preparations is succinate. It is primarily active on serotonin receptors involved in migraine. In particular, it has high affinity for 5-HT_{1B} and 5-HT_{1D} receptors. Activation of these receptors can help to decrease the abnormal functioning of the trigeminal system involved in migraine^[10].

Sumatriptan is available in several different forms, including tablets, needles and nasal spray. This route is useful with some patients because of nausea / vomiting in the acute migraine phase, and may not be able to swallow tablets / capsules. The intranasal route is the administration of the drug inside the nose and the absorption is done by means of the nasal mucosa.

Pharmaceuticals, in this instance sumatriptan, are molecules with the molecular formula C₁₄H₂₁N₃O₂S and molecular weight of ~ 295.40 g/mol (as the free molecule).

It is therefore suitable to use sumatriptan succinate as a drug model for the proposed nasal spray since it is an approved acute migraine medication and is already used as an intranasal medicine. The formulation can be tailored to ensure precision of dosing, good spray properties, acceptable nasal tolerability and rapid rate of drug release^[11].

Table -1: Important Drug Profile

Parameter	Information
Drug	Sumatriptan succinate
Drug class	Triptan
Therapeutic use	Acute migraine
Main receptors	5-HT _{1B} and 5-HT _{1D}
Molecular formula of sumatriptan	C ₁₄ H ₂₁ N ₃ O ₂ S
Molecular weight of sumatriptan	295.40 g/mol
Route of interest	Intranasal
Main action	Reduces migraine-related trigeminal activity

Pharmacology

Sumatriptan is a serotonin receptor agonist belonging to the triptan class. Its pharmacological action is mainly related to stimulation of 5-HT_{1B} and 5-HT_{1D} receptors. The primary pharmacology is related to stimulation of 5-HT_{1B} and 5-HT_{1D} receptors. Such receptors are found in vessels in the brain and in sensory nerve terminals of the trigeminal system. Sumatriptan works by activating these receptors, causing constriction of some blood vessels in the brain and also by blocking the release of pro-inflammatory neuropeptides that play a role in the development of migraine. Serotonin and psilocybin activate 5-HT_{1B} receptors to suppress cortical signaling through the claustrum^[12].

The drug will not come in a box for "prevention" of future migraine attacks, but rather to treat a migraine attack. Sumatriptan is a drug that can be taken in various ways. For the present study the intranasal route is of special interest as it is a route of administration other than the oral route.

There can be differences in the pharmacokinetics depending on the route. The peak plasma concentration after intranasal administration has been reported to be around 20 mg at 1.5 hours, but may vary from individual to individual. The half-life following intranasal administration is ~ 1.8 hours.

Sumatriptan is mainly metabolized in the liver, primarily through the action of monoamine oxidase-A (MAO-A). Most of the dose is metabolized and some of the dose is excreted as the parent compound in the urine^[13].

Table – 2: Pharmacological Profile

Pharmacological property	Description
Drug class	Triptan
Receptor activity	5-HT _{1B} /5-HT _{1D} agonist
Main therapeutic action	Acute migraine relief
Major site of action	Cranial vessels and trigeminal sensory pathways
Main metabolism	Predominantly MAO-A
Intranasal half-life	About 1.8 hours

Mechanism of Action and Therapeutic Potential

In migraine, the trigeminal system is engaged, a system that is linked with structures that have the capacity to cause pain around the brain and around the cranial blood vessels. During migraine attack, sensory nerves can release, for instance, neuropeptides that induce pain and vascular changes. Sumatriptan is a 5-HT_{1B} / 5-HT_{1D} agonist. When these receptors are activated, some blood vessels in the brain constrict and pro-inflammatory neuropeptides are inhibited from being released from the trigeminal sensory nerves. This helps to decrease the activity of pathways involved in the pain of migraine.

Therefore, the therapeutic activity of sumatriptan would rely on its selective activity on some important mechanisms involved in an acute attack of migraine. Nasal formulation is also a potential application of value to patients who cannot swallow an oral medication for migraine because of nausea or vomiting^[14].

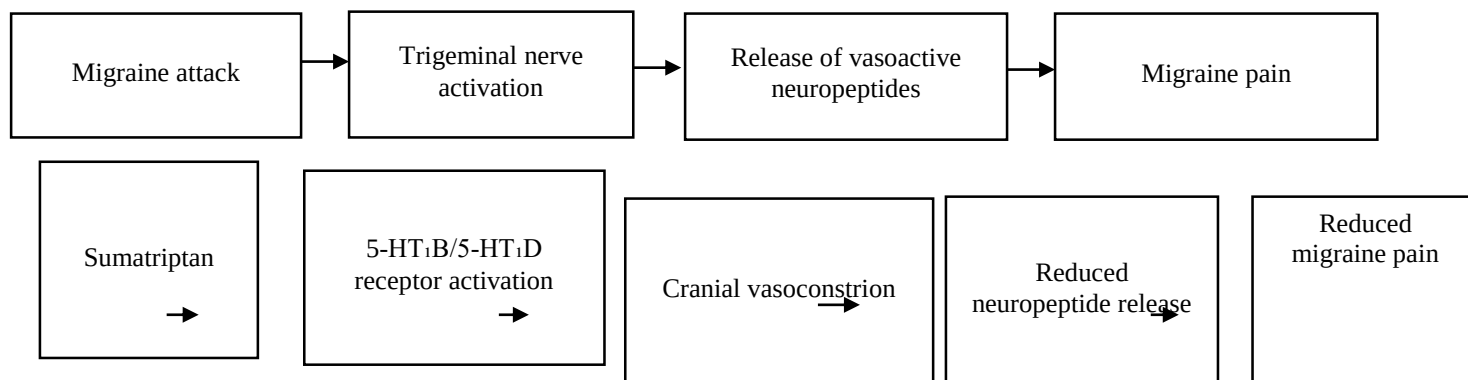
- **Affinity for 5-HT_{1B} receptors** – Action on 5-HT_{1B} Receptors is high for Sumatriptan. Activation of these receptors helps to cause the narrowing of blood vessels in the brain that is a factor in migraine. This vascular action can help decrease the headache aspect of an acute migraine attack. The 5-HT_{1B} receptor activity is thus a therapeutic component of sumatriptan.
- **Action on 5-HT_{1D} Receptors** - Sumatriptan also works on the 5-HT_{1D} receptors located on the sensory nerve endings in the trigeminal system. The receptors are involved in inhibiting the release of substances causing migraine pain. Sumatriptan acts by reducing the release of this neuropeptide and consequently the transmission of pain signals created by a migraine attack.
- **Trigeminal Activity Reduction** - This is important in the development of migraine in the trigeminal system. The sensory nerves in the trigeminal system may play a role in pain and inflammatory signalling during an attack. Sumatriptan works by

decreasing this activity by binding to serotonin receptors. This particular action can be useful to manage the processes involved in the headache and other migraine related processes.

- **Intranasal delivery has potential** - The nasal route is a useful alternative for oral delivery. A nasal spray can be administered straight into the nose, and is a suitable medication for individuals who cannot swallow the tablet due to nausea or vomiting. Therefore, the intranasal formulation of sumatriptan succinate could be a convenient dosage form for acute migraine treatment in the current formulation. It is a clinically relevant route, as evidenced by FDA approved nasal spray formulations of sumatriptan.

- **Therapeutic Potential in Acute Migraine** - Sumatriptan: It can only be used to treat an acute migraine attack and is not indicated for prevention. It's a selective serotonin-receptor activity, which directly impacts key pathways of migraine. Sumatriptan succinate is an established anti-migraine agent with both nasal and oral routes of administration so a model of a nasal spray formulation is a suitable drug model for formulation and evaluation^[15].

Simple Mechanism Flow



Nasal Drug Delivery System

Nasal drug delivery is a technique which entails applying medication through the nose. Here, the drug is sprayed, dropped, formulated in gel, powder or other suitable form into the nose. Many drugs may be absorbed very quickly in the nasal cavity due to its rich blood supply and thin mucosal lining. Hence, nasal route is beneficial for both local and systemic drug delivery. It may be helpful in emergencies where it is necessary to respond immediately.

Nasal spray a dosage of medication is sprayed into the nose. The drug, after administration, will be exposed to the mucous layer and can be absorbed in the mucous layer and enter into the nasal epithelium. Drug absorbed can then go into systemic circulation. As compared with oral delivery, all the problems associated with gastrointestinal degradation and hepatic first-pass metabolism are avoided when a drug is administered nasally. This can aid to guarantee the availability and effectiveness of certain drugs^[16].

Secondly, the nasal route is a non-invasive and convenient route of drug administration since it does not involve the use of needles. Perfect for people who have swallowing difficulties. If a migraine is acute, with nausea and vomiting, it may be difficult to take anything by mouth. Therefore, intranasal administration of sumatriptan succinate formulation could be considered a good alternative to the other routes of administration.

An ideal nasal spray should have the following characteristics: desirable pH, viscosity, drug concentration, drug uniformity, stability and microbiological quality. It should also not be irritating to the nasal mucosa, and not be an unnecessary irritant. The spray device should deliver a uniform dose and deposit the dose in the appropriate area of the nasal cavity.

Formulation and device characteristics are important for the nasal delivery and can provide therapeutic advantage, such as rapid absorption, hepatic bypass and non-invasive delivery^[17].

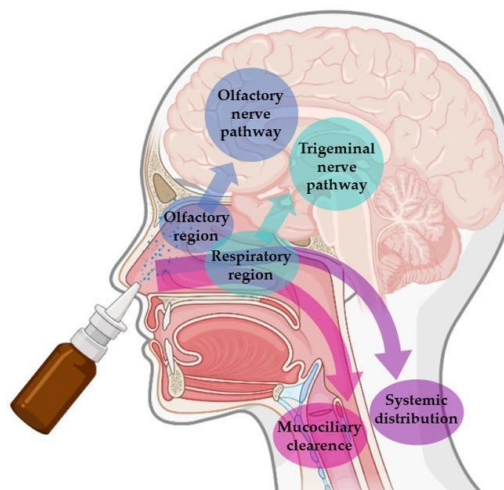


Image -3: Nasal Drug Delivery System

Sources: <https://www.mdpi.com/1999-4923/16/10/1322>

Principles of Nasal Drug Delivery System

The principle behind nasal drug delivery is to target the drug to the nasal mucosa where it will dissolve and penetrate the mucosa. The drug is first distributed on the mucous layer after administration. Then it dissolves and flows towards the epithelial surface. The drug can penetrate the epithelial cells or gaps between cells and into the profusely-vascularized tissue beneath the nasal mucosa. It can then pass to the systemic circulation and to act as a therapeutic agent. The extent of this process is influenced by the properties of the drug like solubility, size, and lipophilicity, pH of the formulation, viscosity, and nasal blood flow and residence time. The formulation can be cleared from the nose by mucociliary clearance, which can also reduce the amount of formulation absorbed. Therefore, the optimum nasal formulation should have adequate release of the drug, good contact with the nose, a uniform dose, be stable and have a low irritating effect^[18].

- **Proper deposition in the nasal cavity** - Correct depositing of the formulation into the nasal cavity is the first step. A nasal spray should produce the proper sized droplet that covers the entire lining of the nose. Good deposition translates to a higher surface area of contact between formulation and absorption site. Thus the nasal device and spray pattern is of critical importance for effective delivery.
- **Drug Dissolution and Absorption** - Once deposited the drug should dissolve in the nasal fluid and be available for absorption. The drug is then dissolved into the nasal epithelium, into the blood vessels below. The nose is extremely vascular and offers a high rate of relative rapid systemic absorption. The molecular size, solubility and lipophilicity of the drugs can be influencing factors in this process.
- **Residence Time and Mucociliary Clearance** - The formulation should be able to have enough time in contact with the mucous membranes of the nose. But the nose has a natural defence mechanism (mucociliary clearance). Mucous secretion and movement continually push it into the throat and it may not be completely absorbed. However, residence time can be extended by using mucoadhesive polymers; but, an increase in the viscosity can cause a corresponding effect on the drug diffusion.
- **Formulation and Nasal Environment** - Formulation needs to be safe, stable and comfortable when in the nasal cavity. Some of the most important factors are pH, viscosity, osmolality, drug concentration, compatibility with the excipients and microbiological quality. The formulation should reduce the amount of irritation and should allow for accurate and reproducible dosing. Congestion of nose, status of mucus and other physiological factors also affect the absorption of drugs^[19].

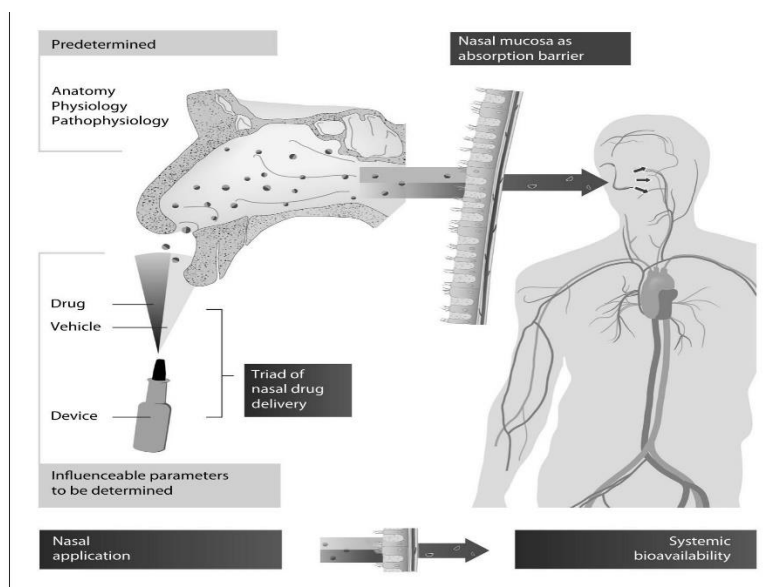


Image- 4: Humans are discovered to possess nasal drug delivery in them.

<https://11nq.com/vo4zhki>

Advantages and Limitations

There are several important advantages of nasal drug delivery to some of the conventional drug delivery paths. It is non-invasive, easy for administration and can be self-administered. The nasal mucosa is well vascularized and is the means by which many drugs are absorbed rapidly. Nasal administration can also bypass the gastrointestinal degradation and hepatic first pass metabolism, and can lead to increased drug availability and decreased dose requirements for some medications. It can be helpful where an immediate action is needed regarding the treatment. The nasal route can be used especially if nausea or vomiting makes it difficult to take the medication by mouth, and may be helpful particularly in acute migraine. However, there are certain restrictions for nasal delivery. Limited amount of drug is given by nasal route. The mucociliary clearance can rapidly remove the drug, and its absorption can be decreased. Certain drugs may be degraded by nasal enzymes and certain excipients may not be suitable for nasal use and may cause irritation. Other factors that can have an impact on drug deposition and absorption include difficulties delivering the medicine, such as nasal congestion, technique, or nasal anatomy.

One of the major benefit of nasal delivery is the potential of rapid absorption of the drug. The nasal mucosa is quite vascular and is relatively permeable. This may provide the drug a way to get into the general circulation without having to go through the gastrointestinal tract. Rapid absorption is beneficial in those situations where a fast action would be required such as during acute migraine attack^[20].

- **Avoidance of gastrointestinal and first-pass effects** – This will prevent drug being exposed to the acid environment of gastrointestinal tract and intestinal metabolism. This also bypasses the "first pass" effect in the liver following oral administration. This is good in the case of drugs that are poorly absorbed in the gut or have a high first-pass metabolism.
- **Convenient and Non-Invasive Administration** – Nasal administration avoids the use of needles, and is relatively easy for patients to use. Nasal spray formulation can help with self-administration of the product and can also be convenient for patients. This is particularly beneficial if tablets are hard to swallow due to nausea, vomiting or other difficulty. Nasal sprays are also widely prescribed, and are easy to use and simple.
- **Limited Dose and Absorption Problems** - One of the drawbacks is the amount of dosage which can be inserted into the nose in one normal dose. The drug, therefore, needs to be potent enough and concentrated enough to be effective. The formulation may also be cleared from the absorption site by mucociliary clearance prior to the uptake of the drug. Additional absorption issues can be seen for poorly permeable and high molecular weight drugs.
- **Nasal Irritation and Physiological Factors** - The nasal mucosa is sensitive and unsuitable formulation ingredients may result in irritation or discomfort. Factors that could influence drug deposition and absorption include nasal congestion, mucous secretions, and sneezing, as well as nasal anatomy. Too much viscosity can extend residence time, but can decrease the diffusion of the drug. Thus the formulation should strike a balance between stability, safety and residence time and drug absorption^[21].

Formulation Development of Sumatriptan Succinate Nasal Spray

The aim of the formulation development of sumatriptan succinate (nasal spray) is to create a stable, safe, effective and patient-friendly formulation for the treatment of acute migraine. Sumatriptan succinate is selected because sumatriptan has been proven to be an effective drug to treat acute migraine. When it is hard to swallow due to nausea or vomiting associated with migraine, the nasal route may be helpful.

The formulation starts with the selection and evaluation of the drug followed by the selection of appropriate pharmaceutical excipients. Purified water is commonly used as the vehicle for aqueous nasal sprays. The formulation needs to be stable and have the correct pH level, as well as providing nasal comfort to the formulation, which can be achieved using a suitable buffer system. The tonicity can be adjusted by adding sodium chloride. A solubility or permeation-enhancing agent may need to be studied in some formulations to achieve a particular formulation objective. Published sumatriptan nasal formulations have included buffered aqueous systems, and newer formulations have included permeation enhancers to enhance absorption^[22].

The method of formulation to be prepared should be uniform in drug content, acceptable viscosity, good spray pattern, acceptable pH and acceptable tolerability to the nose and should show a consistent dose delivery. In addition to evaluating physical appearance, clarity, drug content, in-vitro drug release, stability and microbiological quality should also be evaluated. The final product should optimise the administration and delivery of sumatriptan succinate so that it can be used to rapidly treat acute migraine attacks.

Developing a sumatriptan succinate nasal spray is a step-by-step process, starting with selecting the drug and finalizing the evaluation of the completed nasal product. The main objective is to develop a formulation which is capable of accurate dosing, good nasal deposition, and adequate release of the drug, good stability and minimum irritating^[23].

Selection and Preformulation of Sumatriptan Succinate

Based on its use in the acute treatment of migraine, sumatriptan succinate is chosen as the active pharmaceutical ingredient. Preformulation studies are conducted to assess the physical parameters, drug/solubility, compatibility with excipients and stability of the drug in different conditions. These studies are used to ascertain the ability of the drug to be formulated in an aqueous nasal product.

Selection of Vehicle and Excipients

Processed water may be used as the liquid in an aqueous spray which is inhaled via the nose. To ensure the proper pH and formulation stability, a buffer system can be chosen. May contain sodium chloride for tonicity control. Depending on the formulation purpose, solubility enhancers, permeation enhancers/viscosity modifying agents can be considered. The excipients chosen in published intranasal sumatriptan formulations confirm that the choice of excipients can affect the absorption and nasal tolerability of the drug.

Preparation of Nasal Spray

The correct dose of sumatriptan succinate to be administered is precisely measured and dissolved in the chosen vehicle. These excipients are then added under carefully-controlled mixing conditions. pH and volume adjusted as necessary and appropriate filtration is done as needed. Final product is packaged in a suitable metered nasal spray container. The metered device is very important because the formulation should discharge the same amount of formulation with each actuation. Nasal formulations should also take into account how much product is able to fit in the nose.

Evaluation and Optimisation

Sprayability, appearance, clarity, pH, drug content and dose uniformity, as well as in-vitro drug release of the prepared formulation, should be evaluated. Changes in physical appearance, drug content and other important quality characteristics during storage should be evaluated in stability studies. It is also important to consider nasal tolerability as inappropriate excipients or formulation conditions may result in irritation.

Selection of Optimised Formulation

The optimized batch may be selected depending upon the formulation that has the highest drug content, spray performance, release, stability and nasal compatibility. This step will ensure the final product, a sumatriptan succinate nasal spray, is reproducible, easily used and ready for additional development for the treatment of acute migraine headaches^[24].

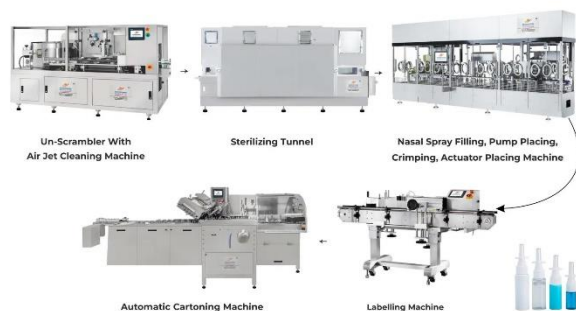


Image -5: Nasal Spray Packaging Line

Sources: <https://sl1nk.com/ym72dfl>



Image- 6: 503B Pharmacy

Sources: <https://11nq.com/f084px6>



Image -7: Nasal Spray Pumps

Sources: <https://11nq.com/a86s243>



Image -8: Complete Nasal Spray Packaging Line

<https://11nq.com/h0q8eu5>

Table- 3: Key formulation parameters

Parameter	Purpose
Drug concentration	Provides the required dose
pH	Supports stability and nasal comfort
Tonicity	Improves compatibility with nasal mucosa
Viscosity	Influences spreading and residence time
Drug content	Confirms formulation uniformity
Spray pattern	Indicates quality of nasal deposition
Dose uniformity	Ensures reproducible dosing
Stability	Confirms quality during storage

Selection of Excipients and Optimization of Nasal Spray Formulation

The selection and optimization of excipients need to be carried out systematically, considering the excipient in the excipient formulation for sumatriptan nasal spray to provide uniform dosing, to be tolerated and acceptable for nasal use, appropriate drug release, stability and consistent spray performance. Significant nasal-spray quality attributes that are mentioned in available guides include: pump delivery, spray content uniformity, droplet size distribution, spray pattern, spray plume geometry, pH, and osmolality. In the development of a Sumatriptan succinate nasal spray, choosing excipients that can affect the solubility, stability, comfort in the nose, residence time and spray performance are important. The formulation should thus be designed in regards to the properties of sumatriptan succinate and its needs on the nasal mucosa.

Appropriate excipients - Purified water can be used as a vehicle in an aqueous nasal spray. It can be used as a suitable medium to dissolve drug and water soluble excipients. The commercial nasal Sumatriptan products are made up of purified water and buffering agents.

Buffering agents can be selected to ensure the correct pH and formulation stability such as phosphate buffers. Commercial available sumatriptan nasal preparations contain a phosphate buffer system. The pH level needs to be selected to ensure the maximum drug stability, nasal tolerability and mucociliary function.

Sodium chloride may be used as a tonicity adjusting agent, but it can be considered in terms of the formulation being comfortable to the nasal mucosa. Nasal formulations should be made around physiological tonicity but this will vary based on the formulation. Increased nasal residence time might warrant research into the use of viscosity modifiers or mucoadhesive agents. These include hydroxypropyl methylcellulose, sodium carboxymethylcellulose and specific mucoadhesive polymers. However, if it is too viscous it may impact the droplet size, spray pattern and dispersion of the drug[25].

Optimisation of the formulation – Optimization involves changing the formulation parameters and observing the effects of the changes in some of the important formulation attributes. The significant factors may be the drug concentration, buffer concentration, pH, tonicity and viscosity. If two or more variables are to be investigated together a systematic approach to experimental design can be employed, such as factorial or response-surface design. These types of designs are used in nasal formulations to explore the interactions of formulation variables on viscosity, droplet size and drug release.

Evaluation of Optimized Formulation - The optimal formulation should be evaluated in terms of its appearance, clarity, pH, osmolality, viscosity, drug content, delivered dose, spray content uniformity, droplet-size distribution, spray pattern and plume geometry. Stability and microbiological quality should also be taken into account where applicable. These tests help to determine consistency and acceptability of nasal formulation.

Selection of Final Batch - It is important to select the final formulation by paralleling all important responses, and not based on only one response. Selection of Final Batch- Drug content, pH and tonicity, adequate viscosity, reproducible spray characteristics, good stability, low potential to cause nasal irritation are the ideal parameters to be considered. Thus the final optimization is a compromise between the performance of the drug, its formulation and the performance and acceptance of the device^[26].

Table- 4: Excipient-selection table

Excipient/Component	Main purpose in nasal spray	Important consideration
Purified water	Vehicle/solvent	Drug solubility and purity
Phosphate buffer	pH control	Nasal compatibility and stability
Sodium chloride	Tonicity adjustment	Patient comfort and osmolality
Viscosity modifier	Residence-time modification	Excess viscosity may affect spray
Mucoadhesive polymer	Increase nasal residence	Must not excessively reduce drug diffusion
Solubility/permeation enhancer	Improve drug availability/absorption	Must be evaluated for nasal safety

These are the choices to consider for formulation development, rather than as a final formulation product. For instance, commercial sumatriptan nasal products employ systems of phosphate buffered aqueous while other intranasal sumatriptan research has pursued the mucoadhesive and permeation enhancing approaches.

Preformulation Studies of Sumatriptan Succinate

Preformulation studies are the initial pharmaceutical studies which are undertaken before the final formulation of the spray. The physical, chemical and pharmaceutical properties of sumatriptan succinate are provided by these studies and are helpful in making a selection of excipients and processing conditions. They play an important role in most nasal formulations as the solubility of the drug, pH, stability, and compatibility can directly impact the formulation performance as well as nasal absorption.

- **Physical Appearance** - Sumatriptan succinate should first be examined for its colour, odour, and physical state and general appearance. According to published chemical databases, Sumatriptan is a solid. Before formulation development it is important that there is a consistent appearance with no visible contamination or changes in appearance. Sumatriptan's reported melting point is ~169-170 °C. These observations give a fundamental knowledge of the nature and identity of the drug.
- To determine the solubility of a drug is an important parameter to develop aqueous nasal spray. The chosen vehicle should have enough solvent to dissolve the drug to give a uniform dose. According to the FDA the sumatriptan succinate is freely soluble in water. Another intranasal study also reveals that sumatriptan succinate is freely water soluble and can be used as a basis for the development of nasal solutions.
- **pH-Dependent Nasal Absorption** - This should be investigated as nasal absorption of sumatriptan succinate is pH dependent. An experimental study published shows that the absorption maximum was seen at pH 5.5 and as the pH increased, the absorption decreased. After 120 minutes, reported absorption was 21.5% at pH 5.5 compared with 17.5% at pH 7.2. Therefore, pH selection cannot be arbitrary, but must be carefully considered and not only related to solubility of the drug.
- **Determination of λ_{max}** - UV-visible spectrophotometry can be used in identification and quantitative estimation of sumatriptan succinate during formulation development, to determine the value of λ_{max} . A literature search indicated a maximum wavelength of either 226–228 nm (depending on the solvent system). The values of approximately 226 nm were obtained in a study performed in water, and approximately 228 and 226.5 nm in acetonitrile and methanol, respectively. The wavelength which is chosen for the analysis must then be verified experimentally for the given method and solvent system used.
- **Drug–Excipient Compatibility** - Drug–excipient compatibility studies are done to determine whether any excipients have a negative interaction with sumatriptan succinate. These methods are commonly used such as Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and, if necessary, X-ray diffraction. FTIR may be helpful for providing useful information for important functional groups, and DSC may be able to identify any changes of thermal behaviour.

In published nasal delivery studies of sumatriptan, FTIR and DSC have been used for the characterisation of drug and formulation components.

- **Nasal Enzymatic Stability** - Additional useful preformulation parameters are the Nasal Enzymatic Stability. In a previously published study, no degradation of the enzyme was observed during the first week of the rat nasal-washing model investigated. This finding opens the door to further studies of nasal delivery, although the results of nasal delivery in animal models does not necessarily apply to human nasal stability.
- **Preformulation Assessment** - The results of these studies help to guide the choice of buffer, tonicity modifier, excipients, and vehicle for the preformulation assessment. The last nasal spray should have good drug solubility, acceptable pH, chemical stability and drug estimation and be compatible with the nasal mucosa. The preformulation results are hence used as scientific criteria to optimize and evaluate sumatriptan succinate nasal spray formulation^[27].

Table -5: Important preformulation parameters

Parameter	Published/expected finding	Importance
Physical state	Solid	Confirms basic drug characteristics
Melting point	~169–170°C	Helps assess thermal behaviour
Water solubility	Freely soluble	Supports aqueous nasal formulation
Nasal absorption pH	Maximum reported at pH 5.5	Helps select formulation pH
UV λ_{max}	~226–228 nm, solvent dependent	Drug estimation
Drug–excipient compatibility	FTIR/DSC recommended	Detects possible interaction
Nasal enzymatic stability	No measurable degradation in first week in one rat model	Supports nasal formulation investigation

Evaluation Parameters for Sumatriptan Succinate Nasal Spray

Evaluation of sumatriptan succinate nasal spray is crucial to ensure quality, safety, stability and performance of the developed formulation. The characteristics of a nasal spray are: Able to deliver the correct dose, distribute the drug evenly throughout the nose, have physical properties and characteristics suitable for intranasal delivery and be reproducible. Some of these parameters can be used to systematically evaluate the prepared formulations^[28].

- **Appearance and clarity** - A visual inspection for colour, clarity and homogeneity should be conducted and any visible particles in the prepared nasal spray should be detected. In an aqueous formulation the formulation should be clear without any foreign material or undesirable precipitates. Additional appearance adjustments should also be documented during storage as this could indicate physical and/or chemical instability.
- **pH** - pH of formulation should be determined with a previously calibrated pH meter. The relevance of pH is that it can cause nasal irritation, and can affect the stability and absorption of the drugs. The pH of the formulation should also be appropriate for balance of the stability of the drug and tolerability in the nose.
- **Drug Content** - Test to ensure product contains proper amount of drug substance (Sumatriptan succinate). The volume of the nasal spray required for analysis is predetermined and diluted in a suitable solvent and analyzed by a validated UV-visible spectrophotometric or chromatographic analysis. The solution is a percentage of the drug label/ theoretical content.
- **Viscosity** - Is determined by using a suitable viscometer. It affects the spreading and residence time of the formulation on the nasal mucosa, its movement. Low viscosity will result in rapid drainage and high viscosity will lead to problems in spray formation and dispersion of the drug ingredients. So it is advisable to use an appropriate viscosity.
- **Drug Release** – In-vitro drug release studies can be carried out to ensure that the amount of sumatriptan released from the nasal formulation in over a period of time. Samples are taken at regular time intervals and tested for the presence of the drug. The release profile can be useful to compare between different batches of formulations and to find the formulation with desired drug release.
- **Delivered Dose Uniformity** - Delivered Dose Uniformity is an important Quality Parameter for a metered Nasal Spray. More than one action should be tested to ensure the device can be used to deliver the same amount of sumatriptan succinate. It is important that there is consistency in dosing because it is easy to over- or under-dose if the dosage varies between different sprays.
- **Spray Pattern** - Spray pattern evaluation is the evaluation of the distribution of the formulation after it is ejected from the nasal spray device. A good spray should give a consistent and even pattern to apply. Appropriate visual or instrument-based method can be used to examine spray pattern. Provides user information about the pump/ nozzle performance.
- **Droplet Size Distribution** - The size of droplets produced by the nasal spray should be determined – droplet size affects deposition inside the nasal cavity. Very large droplets can fall mostly in the front of the nose, very small droplets fall deeper or are inhaled. Thus it is desired to have consistent droplet sizes.
- **pH, Osmolality and Nasal Tolerability** - Osmolality should be measured because it could be a concentrated or diluted formulation and might lead to discomfort. Formulations should also be evaluated as to their potential for nasal irritation. When delivering more than once, the correct pH, osmolality and excipient are key factors to ensure comfort in the nose.
- **Stability Study** - Stability testing should be performed under appropriate storage conditions to determine the changes in the characteristics of appearance, pH, drug content, viscosity and spray performance with time. The formulation should be of the desired quality for the storage period.
- **Microbiological Quality** – The nasal spray may contain water and therefore the microbiological quality needs to be tested. Formulation should comply with the microbial requirements and must not contain any undesirable microbial contamination during use.
- **Overall Evaluation** - All the results from the evaluation should be considered as an overall evaluation to decide on which optimized formulation should be selected. The appearance should be good and reproducible, the pH, the viscosity and the drug

content and delivered dose good and reproducible, the spray pattern and droplet characteristic should be appropriate, drug release should be acceptable, and the drug should be stable and should be nasal tolerable. These parameters collectively set the quality and suitability of the developed nasal spray for further investigation in acute migraine management^[29].

Stability, Safety and Nasal Irritation Studies of the Formulated Nasal Spray

Stability, safety and nasal irritation studies are essential components of the assessment of a sumatriptan succinate nasal spray. The formulation should not produce any undesirable effect on skin after administering, and be physically and chemically stable in storage. Stability testing allows for checking the important parameters like appearance, pH, drug content, viscosity and spray performance to see if they fall within an acceptable range. For a nasal spray, the delivery of the dose over the intended storage time should be constant as well, and this should be guaranteed by a container closure system and pump. The formulation is to be kept under suitable controlled conditions and tested at specified time periods. Note the colour, clarity, precipitation, concentration of the drugs or the characteristic of the spray. Accelerated stability and long term stability studies can be carried out by the application of suitable stability protocol^[30].

- **Physical and Chemical Stability** - Formulated spray should be periodically tested for appearance, clarity, pH, drug content and viscosity. During the study, no significant precipitation, discoloration or change in the amount of the drug should occur. In particular for sumatriptan related nasal products – formulated as aqueous product, it is crucial to control pH and chemical stability.
- **Dose and Spray Stability** - Pump should deliver a consistent volume of formulation over an extended period of time. Thus, spray pattern and uniformity of delivered dose needs to be assessed during stability testing. If the dose of drug is not changed, the change in the pump's performance may lead to a dose change.
- **Microbiological Quality** – Microbial growth can occur in an aqueous nasal spray if not adequately protected; therefore, it is important to monitor the quality for microbiological aspects. Formulation and the container should be tested based on relevant pharmaceutical microbiological specifications. Preservatives if used: their compatibility, effectiveness and tolerability at the nose should also be taken into consideration.
- **Nasal Irritation** - An important safety concern is the direct contact with the nasal mucosa to cause nasal irritation: Irritation can manifest itself as burning, dryness, itching, sneezing, redness or discomfort. Formulation pH, osmolality, excipients, preservatives and repeated exposure may affect the risk. Hence, the formulation needs to be made so that there is minimum unnecessary irritation.
- **Safety assessment** – Assessment of local nasal effects and, if applicable, systemic adverse effects should be included in safety assessment. Clinical trials of intranasal sumatriptan have been published and have shown that the drug is effective and is generally well tolerated, with some minor discomforts such as taste, or local nose symptoms. Therefore, the final formulation should be tested in order to check its therapeutic effect and tolerability^[31].

Therapeutic Effectiveness of Sumatriptan Succinate Nasal Spray in Acute Migraine

Sumatriptan succinate nasal spray is a drug that is used to treat a migraine attack. Sumatriptan is primarily a 5-HT_{1B/5-HT_{1D}} receptor agonist and has an anti-trigeminal neuropeptide releasing and anti-cranial vasodilator activity in the treatment of migraine. An alternative to oral treatment is the nasal route which may be especially helpful when migraine is associated with pain-related nausea or vomiting. Intranasal sumatriptan has been shown to be clinically effective at relieving migraine headache and headache-associated symptoms^[32].

- **Reduction in Headache Intensity** - Reduction in Headache Intensity - Reduction in severity of headache following administration. A clinical study is a study that follows patients for a period of time, such as 30 minutes, 1 hour and 2 hours after treatment. The percentage of treated patients who experience relief from headache or pain that is then compared to the percentage of patients who get relief with a placebo or another treatment.
- **Onset of Action** - Intranasal use has one of the greatest advantages in that the therapeutic effects might occur relatively fast. A systematic review of intranasal sumatriptan trials revealed that there was therapeutic activity as early as 15 minutes after 20 mg (or 10 mg) of intranasal sumatriptan and lasting for 2 hours in acute migraine.
- **Relief of Associated Migraine Symptoms** - The manifestation of migraine can be nausea, sensitivity to light (photophobia) and sound (phonophobia) and headache. Thus, these associated symptoms may be assessed as a part of the clinical assessment of sumatriptan nasal spray. If the headaches have improved along with other symptoms, then this is a better sign of therapeutic effectiveness.
- **Comparison with Oral Sumatriptan** - Alternative to oral sumatriptan, when oral treatment is impractical or not tolerated. There is comparative evidence that both oral and intranasal sumatriptan can be used to treat acute migraine, and the intranasal route could be considered for those who cannot take it by mouth or by injection.
- **Published Clinical Evidence** - In 20 mg intranasal sumatriptan vs placebo study, a significantly larger proportion of sumatriptan were headache-free and had no pain at primary assessment time. Sumatriptan nasal spray was also linked to an improvement in the symptoms of migraine.
- **Evaluation of the Developed Formulation** - If a new nasal spray formulation has been developed, efficacy of the publication of the known nasal spray formulations of the same drug cannot be used to assume the efficacy of the developed formulation. Testing should be determined if deemed necessary, experimental or clinical and the outcomes should be pre-determined. Good measures: percentage of patients who have headache relief, percentage who become pain-free, time to meaningful relief, recurrence of headache, use of rescue medication and adverse effects of the medication. Such results can be employed to determine whether the formulation designed can provide a therapeutic effect.
- **Therapeutic Potential** – From what is currently known from the clinical literature, intranasal sumatriptan is an excellent treatment option for acute migraine. The usefulness depends on the particular pharmacological effect, and, due to the absorption through the nose, it can be used orally if this is not possible. The effectiveness of the specific formulation produced in the present invention however, should be determined in the end by correct formulation, pharmacological evaluation and if applicable, clinical evaluation, and not only by past results obtained with comparable formulations^[33].

CONCLUSION

The present study was shown that development of sumatriptan succinate nasal spray is a promising pharmaceutical approach for the treatment and management of acute migraine. The primary goal was accomplished by formulating, optimizing and systematically testing an intranasal dosage form that would provide a convenient and possibly quick delivery of a drug. Sumatriptan succinate has proven effective in the treatment of acute migraine, and is also an effective agonist at the serotonin receptors 5-HT_{1B} and 5-HT_{1D}, which play a role in inhibiting trigeminal activity and, hence, migraine related pain.

Development of an aqueous nasal formulation, with the incorporation of suitable pharmaceutical ingredients (purified water, buffer and tonicity adjusting agents), and the use of viscosity and/or permeation modifiers (if required). A comprehensive analysis of appearance, pH, viscosity, drug content, uniformity of drug delivery, spray pattern, droplet size distribution, drug release, stability and microbiological quality. These parameters are important for reproducible dosing and formulation stability and acceptable nasal performance.

Intranasal sumatriptan's therapeutic use. Nasal administration might be a useful alternative in patients who are unable to swallow, because of nausea/vomiting or dysphagia, as well as being known to have a pharmacological effect, which might make it a useful treatment in the acute management of migraine.

Overall, the study indicates that the optimized Sumatriptan succinate nasal spray may be a promising noninvasive dosage form that is convenient and may be rapidly administered. The therapeutic efficacy of the particular formulation should, however, be demonstrated by appropriate experimental, pharmacological and clinical testing and not inferred from previously marketed formulations.

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