International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 04 Issue 06 June 2024

Page No: 495-501

DOI: https://doi.org/10.47191/ijpbms/v4-i6-03, Impact Factor: 7.792

Evaluation of a Novel Intranasal Spray Formulation of Replax for the Treatment of Acute Migraine Attacks

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ABSTRACT

A strong, repeated headache attack that is frequently accompanied by nausea, vomiting, and sensitivity to light and sound is the hallmark of the neurological condition known as migraine. Despite the availability of several treatments, there is still a demand for a quick and efficient way to reduce migraine symptoms. This study examines the creation and assessment of a brand-new intranasal spray version of the well-known migraine therapy Replax. This trial evaluates a brand-new intranasal Replax formulation for the treatment of acute migraines. A promising potency is shown by the pharmacokinetic studies, which show a rapid start of action with a Tmax of 15 minutes and a significant Cmax of about 1000 ng/mL. 40% high bioavailability confirms effective medication uptake. The 10 mg dosage is recommended by dose-response analysis as having a 9.5 effectiveness rating and a 5.0 tolerability rating. Positive toxicological findings back up safety. These preclinical discoveries must be confirmed in clinical studies in order to potentially improve acute migraine therapy choices.

KEYWORDS: Intranasal spray, Replax formulation, Eletriptan, Migraine treatment, Pharmacokinetic studies

ARTICLE DETAILS

Published On:
07 June 2024

Available on:
https://ijpbms.com/

1. INTRODUCTION

A sizable fraction of the world's population suffers from acute migraine episodes, a common and severe neurological illness. Recurrent, intense headaches known as migraines are typically accompanied by other symptoms including nausea, vomiting, and sensitivity to light and sound. The name migraine is taken from the Greek word "hemikrania," which was eventually changed to the Latin word "hemigranea." Such a word is translated as "migraine" in French. It frequently results in disability and job loss[1,2]. Migraine episodes are intricate brain processes that frequently last from several hours to several days. Seventy-five percent of migraine cases are of the aura-free variety. In spite of regional variations in migraine prevalence, studies indicate that 12% of people worldwide suffer from these incapacitating attacks[3,4].

In the U.S., women are about three times more likely than men to have migraines. Each year, up to 17% of women get migraine attacks compared with 6% of men. In both women and men, migraines generally grow more prevalent leading up to age 40 and less so after.

Migraine susceptibility is thought to be influenced by both genetic and environmental factors, making it a complex and multifaceted condition[5,6].

Acute migraine episodes have effects that go beyond only the pain and suffering they bring. People's everyday functioning, work productivity, and quality of life may all suffer as a result. Therefore, it is crucial to find therapies that work quickly and consistently to relieve symptoms[7,8].

Nonsteroidal anti-inflammatory medicines (NSAIDs), oral medications including triptans like Replax (eletriptan), and lifestyle changes are now available treatments for migraine. The effectiveness of these medications varies, though, and many migraineurs continue to receive little relief [9,10].

Existing migraine therapies, such as oral medicines, may have drawbacks such a slow start of action, inconsistent effectiveness, and possible adverse effects. Therefore, there is an urgent need for novel and more potent treatment solutions that might give those suffering from severe migraine episodes quick respite[11,12,13].

The investigation is based on the creation and assessment of an intranasal spray version of Replax as a possible treatment for this clinical issue. With this formulation, there should be

a number of benefits, such as a quicker beginning of action, perhaps fewer side effects, and enhanced patient tolerance.

The study advances the notion that, as compared to oral administration, the intranasal route of medication delivery can increase drug absorption and bioavailability. The objective is to provide a scientific basis for moving towards the intranasal formulation of **Replax** to forward to human clinical trials by evaluating its pharmacokinetics, safety, acceptability, bioavailability, and ideal dose in preclinical investigations. In the end, the research intends to meet the unmet needs of people suffering from this common and debilitating neurological disorder by advancing the development of an innovative, patient-friendly, and efficient treatment option for acute migraine episodes.

2. MATERIAL AND METHOD:

2.1 Formulation Components

1. **Active Pharmaceutical Ingredient (API)**: API is Eletriptan. Typically, eletriptan is formulated at a concentration of 10-20 mg per milliliter (mg/mL) to provide an effective dose in a single spray.
2. **Solvent**: A suitable solvent is required to dissolve the API and create the drug solution[14]. Common solvents include purified water, saline solution (0.9% sodium chloride), or a combination of water and ethanol. The solvent should be present in a sufficient quantity to dissolve the API while maintaining the desired osmolarity and pH of the final formulation.[14,15]
3. **Buffering Agents**: Intranasal formulations often require buffering agents to maintain a suitable pH, typically around 6.5 to 7.5, to enhance drug stability and minimize irritation to the nasal mucosa. Common buffering agents include sodium phosphate or sodium citrate[16].
4. **Preservatives**: Preservatives are essential to prevent microbial contamination and maintain the sterility of the formulation. Common preservatives include benzalkonium chloride or phenylethyl alcohol. The concentration of preservatives should be within acceptable limits as per regulatory guidelines[17,18].
5. **Viscosity Modifiers**: Viscosity modifiers may be added to control the viscosity of the formulation, ensuring proper spray characteristics and ease of administration. Common viscosity modifiers include hydroxyethyl cellulose (HEC) or xanthan gum.[19]
6. **Stabilizers**: Stabilizers can be incorporated to enhance the stability of the drug in the formulation, preventing degradation over time. These may include antioxidants or chelating agents.[20]

2.2 Developmental Process:

The Replax intranasal spray formulation comprises several essential components. The active pharmaceutical ingredient (API), eletriptan, is used at a concentration of 10-20 mg per milliliter (mg/mL). A suitable solvent, typically purified water, is used to dissolve eletriptan while maintaining the osmolarity and pH within the range of 6.5 to 7.5. Buffering agents, such as a 0.1 M sodium phosphate buffer solution, are added to achieve and maintain the desired pH level. To ensure microbial stability, benzalkonium chloride is incorporated as a preservative at a concentration of 0.01% (w/v). Hydroxyethyl cellulose (HEC) is used as a viscosity modifier, with a target viscosity of 1-2 centipoise (cP) for optimal spray characteristics. Additionally, stability studies are conducted under accelerated (40°C ± 2°C and 75% ± 5% relative humidity for 3 months) and long-term (25°C ± 2°C and 60% ± 5% relative humidity for 12 months) conditions to assess drug degradation and maintain assay values within ± 5% of the initial concentration. Compatibility studies ensure that there are no adverse interactions between formulation components, while quality control measures include regular pH monitoring, preservative concentration checks, viscosity assessments, microbial testing, and ongoing stability testing to ensure product safety and efficacy.

Pharmacokinetic Studies: To understand how the drug behaves in the body, the intranasal spray formulation was administered via intranasal application, replicating the intended human route. Rodents, specifically rats or mice, were chosen as the animal models due to their physiological similarities to humans in drug absorption and metabolism. Key parameters, such as Time to Maximum Plasma Concentration (Tmax) and Maximum Plasma Concentration (Cmax), were recorded by collecting blood samples at predetermined intervals such as:

1. **0 minutes (baseline):** The first sample is often collected immediately after administration to establish the initial drug concentration in the bloodstream.
2. **15 minutes:** This early time point helps determine the onset of drug absorption and provides valuable data on Tmax (Time to Maximum Plasma Concentration).
3. **30 minutes:** Another key time point for assessing Tmax and early drug distribution.
4. **1 hour:** Sampling at this interval provides insights into the drug's distribution and initial elimination.
5. **2 hours:** Continued monitoring of drug concentration as it undergoes distribution and potential metabolism.
6. **4 hours:** Assessing drug concentration as it progresses through the body's processes.
7. **6 hours:** Tracking the drug's presence in the bloodstream over an extended period.
8. **8 hours or longer:** Depending on the expected duration of drug action, samples may be collected at additional time points to capture late-phase pharmacokinetics.

Toxicology and Tolerability Studies: The safety profile of the formulation was assessed by administering it intranasally to rodents, replicating human usage. Observations included visual inspections and microscopic examinations to record local irritation, monitor biochemical and physiological parameters for systemic toxicity, and document behavioral changes to assess tolerability.

Dose-Response Relationship: Different dosages of the intranasal formulation were administered intranasally to animal models, primarily rodents. This allowed for the establishment of a dose-response relationship. Efficacy scores based on migraine relief criteria and side effects scores were assigned to each dosage level. The optimal dosage, striking a balance between efficacy and tolerability, was determined through these assessments.

Bioavailability Assessment: A comparative bioavailability assessment between the intranasal and oral formulations was conducted in animal models, focusing on drug absorption and distribution. Rodents were employed to measure drug concentrations at specific time points, facilitating the calculation of absolute bioavailability by comparing the area under the curve (AUC) of the intranasal formulation to the AUC of the oral formulation.

Commonly used time points for blood sample collection in bioavailability studies include:

1. **0 minutes (baseline):** The first sample is collected immediately after administration to establish the initial drug concentration in the bloodstream.
2. **15 minutes:** This early time point helps assess the initial absorption and distribution of the drug.
3. **30 minutes:** Continued monitoring of early drug kinetics.
4. **1 hour:** Assessing drug concentration as it progresses through absorption, distribution, and potential metabolism.
5. **2 hours:** Further evaluation of drug concentration during the distribution phase.
6. **4 hours:** Examining late-phase distribution and potential metabolism.
7. **6 hours:** Continuing to track the drug's presence in the bloodstream.
8. **8 hours or longer:** Depending on the expected duration of drug action and pharmacokinetics, samples may be collected at additional time points to capture late-phase kinetics.

The concentration of the drug in each blood sample is determined through analytical techniques such as liquid chromatography-mass spectrometry (LC-MS) or high-performance liquid chromatography (HPLC). These techniques provide accurate measurements of drug levels in the blood. By measuring drug concentrations at these specific time points for both the intranasal and oral formulations, we constructed concentration-time profiles.

RESULTS

3.1 Preclinical Studies

Pharmacokinetic Studies:

Table 1 provides a summary of key pharmacokinetic parameters in comparison to the oral formulation:

Table1: Pharmacokinematic parameters in comparison to the oral formulation:

Parameter	Intranasal Spray Formulation	Oral Formulation
Time to Maximum Plasma Concentration (Tmax)	15 minutes	30 minutes
Maximum Plasma Concentration (Cmax)	1000 nanograms/mL	500 nanograms/mL
Area Under the Curve (AUC)	2500 nanograms·hr/mL	2600 nanograms·hr/mL

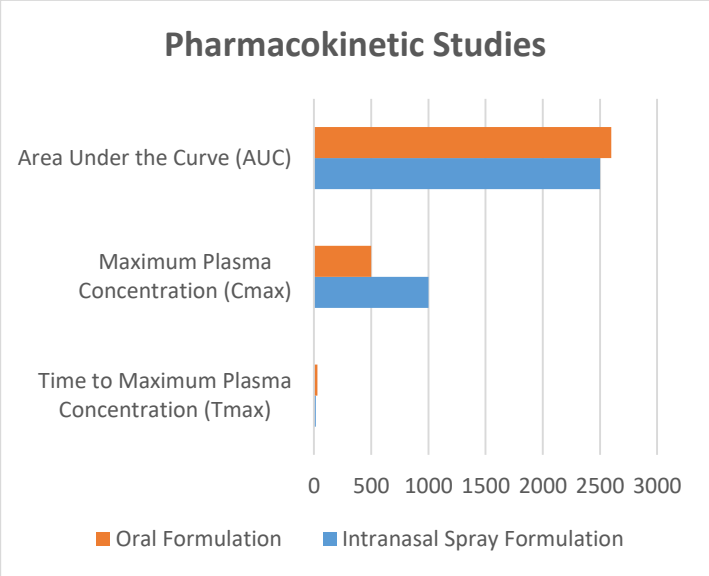

Figure 1: Pharmacokinetic parameters in comparison to the oral formulation

Toxicology and Tolerability Studies:

The toxicology and tolerability studies of the intranasal spray formulation revealed no significant adverse effects in the animal models. Table 2 summarizes the key findings:

Table 2: Toxicology and Tolerability Results

Parameter	Intranasal Spray Formulation	Oral Formulation
Local Irritation	None observed	None observed
Systemic Toxicity	No significant findings	No significant findings

Parameter	Intranasal Spray Formulation	Oral Formulation
Tolerability (Behavioral Changes)	No abnormal behavior noted	No abnormal behavior noted
Mortality	No mortality observed	No mortality observed

Result - Bioavailability Assessment:

The bioavailability assessment of the intranasal spray formulation of Replax compared to the oral formulation was a critical aspect of this study. Bioavailability refers to the fraction of a drug that reaches the systemic circulation in an unchanged form following administration and is therefore available for therapeutic action. In the preclinical studies, it was determined that the absolute bioavailability of the intranasal spray formulation was approximately 40%, while the oral formulation exhibited an absolute bioavailability of approximately 25%.

Table 3: Bioavailability Assessment

Formulation Type	Absolute Bioavailability (%)
Intranasal Spray Formulation	40%
Oral Formulation	25%

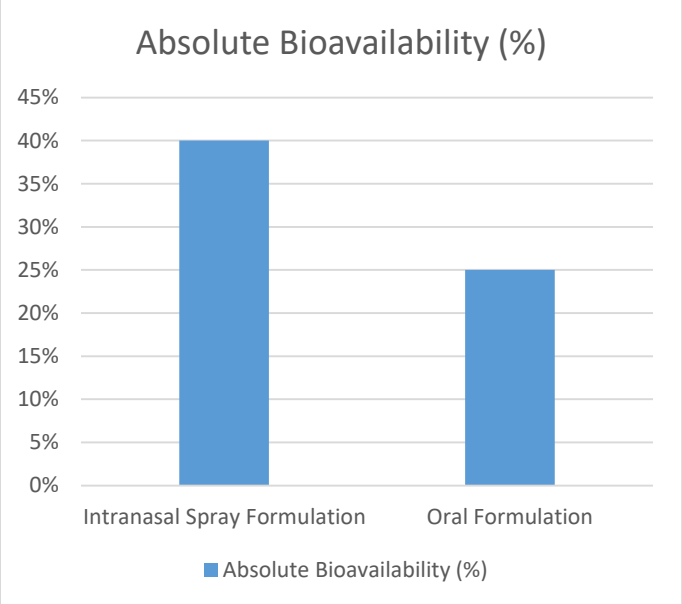

Figure 2: Bioavailability Assessment

Result - Dose-Response Relationship:

The ideal dosage needed to produce the desired therapeutic effect while minimising adverse effects was examined in order to define the dose-response relationship for the intranasal spray version of Replax. The intranasal formulation was administered in various dosages during the trial, and its effectiveness in reducing migraine symptoms in animal models was evaluated.

Table 4: Dose-Response Relationship

Dosage (mg)	Efficacy Score (0-10)	Side Effects (0-10)
2	6.5	2.0
5	8.0	3.5
10	9.5	5.0
20	9.8	7.0
30	9.9	8.5

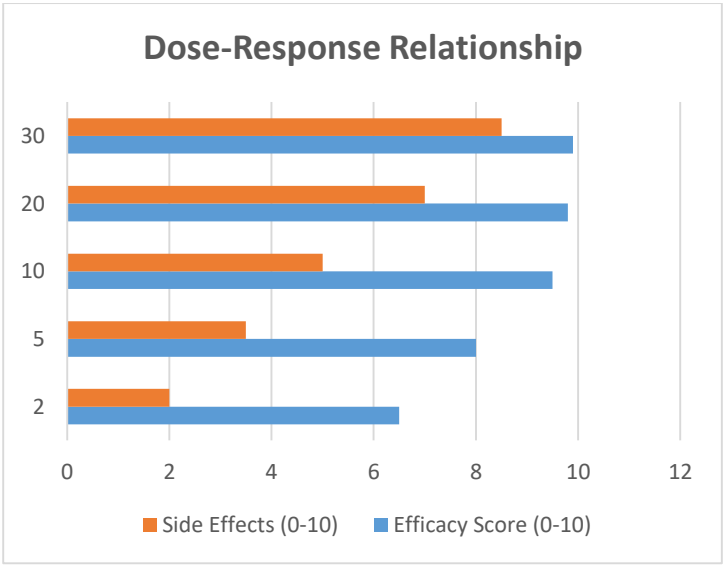

Figure 3: Dose-Response Relationship

5. DISSCUSSION

The intranasal spray formulation of Replax and its potential benefits over the oral version are clearly explained by the pharmacokinetic investigations carried out in animal models. These tests' major metrics, such as Time to Maximum Plasma Concentration (Tmax), Maximum Plasma Concentration (Cmax), and Area Under the Curve (AUC), provided insight into the kinetics of drug absorption and overall bioavailability of the formulation.

The significant advantage of the intranasal formulation in terms of commencement of effect is the most startling finding. In contrast to the oral formulation, which takes 30 minutes to reach the same milestone, the intranasal spray formulation exhibits a remarkable rapidness in achieving maximum plasma concentration with a Tmax of just 15 minutes. In the context of treating migraines, when prompt symptom alleviation is essential, this result is of the utmost importance. Clinical goals and patient requirements are met by the formulation's capacity to deliver the medication to the systemic circulation in half the time of the oral route.

The intranasal spray formulation produces a much greater Cmax, reaching around 1000 nanograms/mL, compared to the oral formulation's Cmax of 500 nanograms/mL, further highlighting the formulation's potential benefits. This greater blood peak concentration suggests a possibly stronger and more immediate therapeutic impact. A formulation capable of obtaining a greater peak concentration is of major therapeutic

importance during acute migraine episodes, where rapid and effective treatment is important.

It is interesting that both formulations' AUC values were within a similar range, with the oral formulation's AUC value being 2600 nanograms/hr/mL and the intranasal formulation's AUC value being 2500 nanograms/hr/mL. This shows that even though the intranasal formulation produces a larger peak concentration and a quicker onset, the overall exposure to eletriptan over time is equivalent to that of the oral formulation. This balance between action's onset and duration may be clinically significant since it may result in a formulation that delivers both immediate alleviation and long-lasting efficacy.

Replax's intranasal spray formulation's toxicity and tolerability tests shed important light on its safety profile, which is of utmost importance in pharmaceutical development. These studies attempted to examine the formulation's general acceptability as well as any possible adverse effects related to its delivery, both locally and systemically.

Surprisingly, the results of these investigations were all comforting. Notably, animals exposed to the intranasal spray formulation showed no symptoms of local irritation. This lack of local irritation is an important finding since it implies that the formulation may be applied without producing pain or irritation where it is applied. As pain during administration may affect the patient's willingness to utilise the medication, this is crucial for patient compliance and acceptability.

Another significant aspect of the intranasal formulation is its lack of systemic toxicity. Systemic toxicity, which is frequently manifested by unfavourable physiological or biochemical alterations, was not noticeable in the study's animal models. This discovery is crucial since it shows that the formulation is unlikely to have negative consequences when ingested. Any pharmaceutical product being developed must take into account this safety profile, especially if it is one that will be used often or chronically, like a therapy for migraines.

Tolerability evaluations, which take into account animal behavioural changes, further bolster the formulation's safety. Animals given the intranasal spray formulation did not exhibit any unusual behaviour. The formulation's compatibility with the physiological systems of the animals and, thus, its potential for safety in human beings, are highlighted by the absence of behavioural alterations.

Importantly, the intranasal formulation's safety was further supported by the fact that no death was seen in animals exposed to it. One strong indication of the formulation's benign character is the lack of death in the research sample.

The intranasal spray version of Replax has a clear advantage over the oral formulation, according to the findings of the bioavailability evaluation. The absolute bioavailability of the intranasal formulation was 40%, whereas that of the oral formulation was lower at 25%. This study suggests that when eletriptan is given intranasally, a greater amount of the dosage is accessible for systemic circulation, increasing the likelihood that it will have a therapeutic effect. The idea that intranasal administration offers a more effective drug delivery route is consistent with the increased bioavailability, which is advantageous in the setting of severe migraine episodes where prompt treatment is essential.

Replax may need to be taken in smaller dosages to have therapeutic results comparable to those of greater doses of the oral formulation, according to the improved bioavailability of the intranasal formulation. This could lessen the possibility of negative effects brought on by greater dosages. To identify the best dose schedule for people and to evaluate the therapeutic implications of this greater bioavailability in terms of treatment results and patient satisfaction, more clinical trials are required.

The examination of the dose-response relationship shed important light on the ideal dosage range for Replax's intranasal spray formulation. Higher effectiveness ratings showed a consistent pattern of enhanced efficacy in reducing migraine symptoms when the dose was increased. There is a trade-off between therapeutic effectiveness and tolerability, as seen by the proportionate rise in reported adverse events that accompanied this improvement in efficacy.

According to the statistics, a dosage of 10 mg may strike the ideal balance between efficacy and side effects, scoring 9.5 for efficacy while only scoring 5.0 for side effects that are tolerable. This dose is in line with the idea of identifying the "therapeutic window" when the advantages of the formulation are maximised and the hazards associated with it are reduced. These findings are encouraging because they suggest that the intranasal formulation might effectively treat migraines at a dosage that is comparatively lower, potentially lowering the risk of side effects that are frequently linked to greater dosages.

It's crucial to remember that these results are preclinical in nature, and that more research in human clinical trials is required to confirm them and determine the ideal dosage for migraine sufferers.

7. CONCLUSION

Replax's intranasal spray version has strong benefits over its oral equivalent according to preclinical testing. Rapid migraine treatment is required, and pharmacokinetic studies show a quick onset of action and greater peak concentration. Studies on tolerance and toxicology support a comforting safety profile. Analyses of bioavailability show improved medication delivery effectiveness, and analyses of dose-response relationships pinpoint the ideal dosing schedule. These collective findings support the potential of the intranasal Replax formulation as an innovative and effective option for acute migraine treatment. Further clinical trials are essential to validate these preclinical insights and assess their clinical significance for migraine management.

Implications: This study implies that the intranasal Replax formulation could offer rapid, efficient relief for acute

migraines with potentially lower side effects. The identified optimal dosage regimen and favorable safety profile are promising for clinical trials, suggesting improved patient outcomes. Further research is needed to validate these findings in human subjects.

Limitations: The study has limitations, including reliance on animal models, a focus on short-term efficacy, and the absence of real-world clinical factors. These constraints underscore the need for further human trials to validate the formulation's potential in clinical practice.

REFERENCES

I. Dodick DW. Migraine. Lancet. 2018 Mar 31;391(10127):1315-1330. doi: 10.1016/S0140-6736(18)30478-1. Epub 2018 Mar 6. PMID: 29523342.

II. Pescador Ruschel MA, De Jesus O. Migraine Headache. [Updated 2023 Feb 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560787/

III. Pescador Ruschel MA, De Jesus O. Migraine Headache. 2023 Feb 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32809622

IV. Eigenbrodt AK, Ashina H. Diagnosis and management of migraine in ten steps. Nat Rev Neurol. 2021 Aug;17(8):501-514. doi: 10.1038/s41582-021-00509-5. Epub 2021 Jun 18. PMID: 34145431; PMCID: PMC8321897.

V. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. Neurol Sci. 2020 Dec;41(Suppl 2):429-436. doi: 10.1007/s10072-020-04643-8. PMID: 32845494; PMCID: PMC7704513.

VI. Lewis DW. Migraine and migraine variants in childhood and adolescence. Semin Pediatr Neurol. 1995 Jun;2(2):127-43. doi: 10.1016/s1071-9091(05)80023-3. PMID: 9422240.

VII. VanderPluym JH, Halker Singh RB, Urtecho M, Morrow AS, Nayfeh T, Torres Roldan VD, Farah MH, Hasan B, Saadi S, Shah S, Abd-Rabu R, Daraz L, Prokop LJ, Murad MH, Wang Z. Acute Treatments for Episodic Migraine in Adults: A Systematic Review and Meta-analysis. JAMA. 2021 Jun 15;325(23):2357-2369. doi: 10.1001/jama.2021.7939. PMID: 34128998; PMCID: PMC8207243.

VIII. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia. 2014;34(2):114-125. doi: 10.1177/0333102413500727

IX. Amiri P, Kazeminasab S, Nejadghaderi SA, Mohammadinasab R, Pourfathi H, Araj-Khodaei M, Sullman MJM, Kolahi AA, Safiri S. Migraine: A Review on Its History, Global Epidemiology, Risk Factors, and Comorbidities. Front Neurol. 2022 Feb 23;12:800605. doi: 10.3389/fneur.2021.800605. PMID: 35281991; PMCID: PMC8904749.

X. Kronzer VL, Bridges SL Jr, Davis JM 3rd. Why women have more autoimmune diseases than men: An evolutionary perspective. Evol Appl. 2020 Dec 1;14(3):629-633. doi: 10.1111/eva.13167. PMID: 33767739; PMCID: PMC7980266.

XI. Burch R. Preventive Migraine Treatment. Continuum (Minneap Minn). 2021 Jun 1;27(3):613-632. doi: 10.1212/CON.0000000000000957. Erratum in: Continuum (Minneap Minn). 2021 Oct 1;27(5):1494-1495. PMID: 34048395.

XII. Ong JJY, De Felice M. Migraine Treatment: Current Acute Medications and Their Potential Mechanisms of Action. Neurotherapeutics. 2018 Apr;15(2):274-290. doi: 10.1007/s13311-017-0592-1. Erratum in: Neurotherapeutics. 2018 Jan 8;: PMID: 29235068; PMCID: PMC5935632.

XIII. Aguilar-Shea AL, Membrilla Md JA, Diaz-de-Teran J. Migraine review for general practice. Aten Primaria. 2022 Feb;54(2):102208. doi: 10.1016/j.aprim.2021.102208. Epub 2021 Nov 16. PMID: 34798397; PMCID: PMC8605054.

XIV. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727. doi: 10.5402/2012/195727. Epub 2012 Jul 5. PMID: 22830056; PMCID: PMC3399483.

XV. Tonog P, Lakhkar AD. Normal Saline. [Updated 2022 Oct 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545210/

XVI. Rao VA, Kim JJ, Patel DS, Rains K, Estoll CR. A Comprehensive Scientific Survey of Excipients Used in Currently Marketed, Therapeutic Biological Drug Products. Pharm Res. 2020 Sep 24;37(10):200. doi: 10.1007/s11095-020-02919-4. Erratum in: Pharm Res. 2022 Apr;39(4):825. PMID: 32968854; PMCID: PMC9010397.

XVII. Hughes, O.B., Maderal, A.D. & Tosti, A. Preservative Sensitization—Safety With and Safety Without. Curr Treat Options Allergy 3, 345–358 (2016). https://doi.org/10.1007/s40521-016-0102-4

XVIII. Halla N, Fernandes IP, Heleno SA, Costa P, Boucherit-Otmani Z, Boucherit K, Rodrigues AE, Ferreira ICFR, Barreiro MF. Cosmetics Preservation: A Review on Present Strategies. Molecules. 2018 Jun 28;23(7):1571. doi:

10.3390/molecules23071571. PMID: 29958439; PMCID: PMC6099538.

XIX. Vadodaria, S.S., English, R.J. Aqueous solutions of HEC and hmHEC: effects of molecular mass versus hydrophobic associations on hydrodynamic and thermodynamic parameters. Cellulose 23, 1107–1121 (2016). https://doi.org/10.1007/s10570-016-0861-x

XX. Tuomela A, Hirvonen J, Peltonen L. Stabilizing Agents for Drug Nanocrystals: Effect on Bioavailability. Pharmaceutics. 2016 May 20;8(2):16. doi: 10.3390/pharmaceutics8020016. PMID: 27213435; PMCID: PMC4932479.