

# Migraine Disorders: Pathophysiology and Emerging Liposomal Drug Delivery Approaches

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## ABSTRACT

Migraine is a complicated neurovascular condition that significantly impairs quality of life and productivity, affecting over one billion individuals worldwide. While conventional therapies such as NSAIDs, triptans, and ergot derivatives provide temporary relief, their effectiveness is sometimes limited by low brain penetration, delayed onset of action, and systemic side effects. Liposomes, which are nanoscale vesicles capable of encapsulating both hydrophilic and lipophilic drugs, have emerged as an effective drug delivery system for overcoming these limitations. This review discusses the pathophysiology of migraine, conventional pharmacological approaches, and the limits of existing treatments. It then explores the classification, composition, and mechanism of liposomes, emphasizing the benefits in brain-targeted delivery. The focus is placed on recent preclinical advances demonstrating various liposomal formulations such as sumatriptan, zolmitriptan, propranolol, and natural compounds delivered through intranasal, intravenous, and transdermal routes. These studies showed increased bioavailability, targeted delivery, prolonged release, and improved therapeutic outcomes in experimental models. Liposomes present a compelling approach for the treatment of acute and preventive migraines, bridging the gap between patient safety and efficient drug action.

**Keywords:** Brain-targeted delivery, Liposomes, Migraine, Pathophysiology, Sumatriptan.

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## INTRODUCTION

Migraine is a neurological condition that is defined by recurring, intense headaches, usually of unilateral and pulsating quality, variably followed by nausea, vomiting, phonophobia, and photophobia. These episodes, referred to as migraine attacks, can last from a few hours to several days and significantly affect individuals' daily functioning and quality of life.<sup>1</sup>

Recent findings from the Global Burden of Disease Study 2021 indicate that migraine affects over 1 billion individuals globally and ranks among the leading causes of Years Lived with Disability (YLDs). It is recognised as the second largest cause of disability worldwide and the leading cause among young adult women.<sup>2</sup> In India, migraine prevalence seems to be higher than the global average. A 2023 population-based study conducted in the Delhi National Capital Region reported 1-year migraine prevalence of 26.3%, and a similar figure of 25.2% in Karnataka.<sup>3</sup>

Migraines are a common condition, but their pathophysiology is complex and incompletely understood, which has limited the

development of effective, targeted therapies.<sup>4</sup> Emerging studies suggest that the pathophysiology of migraine involves changes in the brainstem with its interaction with the trigeminal nerve, including imbalances and dysregulation in neurotransmitters and neuropeptides such as serotonin and Calcitonin Gene-Related Peptide (CGRP).<sup>5</sup> Generally, the treatment of migraine involves the use of triptan receptor agonists, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), or pain relievers. However, the administration of these anti-migraine drugs in conventional oral pharmaceutical dosage forms has various challenges, since numerous molecules have difficulty in passing the Blood-Brain Barrier (BBB), which leads to low bioavailability. Other problems associated with these treatments are delayed onset of action, frequent dosing, non-specific distribution, and significant side effects.<sup>6</sup>

To address these limitations, researchers are exploring innovative drug delivery methods. One promising approach is the use of liposomes, due to their ability to encapsulate both water-soluble and lipid-soluble drugs. Liposomes are spherical vesicles made up of one or more phospholipid layers.<sup>7</sup>

This review will discuss the current progress and therapeutic potential of the liposome-based drug delivery system for migraine treatment. It also highlights the preclinical research, formulation strategies and future directions in clinical translation.



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## Pathophysiology of Migraine

Migraine pathophysiology is complicated and includes complex neuroinflammatory and neurovascular processes. The trigeminovascular system activation, dysregulation of neuropeptides like CGRP and PACAP, and neurotransmitters such as serotonin contribute to migraine onset and progression. Understanding these mechanisms is crucial for developing effective treatment techniques.<sup>8</sup>

## Trigeminovascular System Activation

When the trigeminovascular pain pathways are activated, they trigger the release of neuropeptides, such as (PACAP) Pituitary Adenylate Cyclase-Activating Polypeptide and (CGRP), within the dura mater. This release results in vasodilation and neurogenic inflammation. This process sensitises nociceptive pathways, leading to the intense pain of migraine.<sup>9</sup> Figure 1 illustrates the involvement of the trigeminovascular system in migraine.

## Role of Neuropeptides in Migraine

### Calcitonin Gene-Related Peptide (CGRP)

Calcitonin Gene-Related Peptide (CGRP) plays a key role in migraine pathophysiology, contributing to both vasodilation and neurogenic inflammation.<sup>10</sup> Increased CGRP levels in the cranial circulation have been frequently observed during migraine attacks, and these concentrations have been found to correlate with the intensity of headache symptoms.<sup>11</sup> CGRP shows its vasodilatory effects by binding to a specific receptor complex made up of the Calcitonin Receptor-Like Receptor (CLR) and Receptor Activity-Modifying Protein 1 (RAMP1), which are located on smooth muscle and glial cells.<sup>12</sup> Figure 2 illustrates the involvement of the CGRP and trigeminal system in migraine.

### Substance P and Neurokinin A

Substance P (SP) is a part of the Tachykinin (TAC) family of neuropeptides and is encoded by the TAC1 gene. SP carries out its biological effects by binding to G protein-coupled Neurokinin Receptors (NKRs), specifically NK1R, NK2R, and NK3R.<sup>13</sup> SP primarily binds to the NK<sub>1</sub> receptors, causing vasodilatation, mast cell degranulation, and the release of inflammatory mediators. Neurokinin A (NKA) is a neuropeptide like SP and belongs to the tachykinin family. NKA is co-released with substance P and binds to NK2 receptors. NKA contributes to dural plasma protein extravasation and modulation of nociceptive signalling.<sup>14</sup>

### Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)

Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP), a neuropeptide from the glucagon/secretin family, has been recognised as a key factor in the complicated neurovascular mechanisms of migraine.<sup>15</sup> It appears in two biologically active forms, PACAP-38 and PACAP-27, with PACAP-38 being the

dominant in humans.<sup>16</sup> It shows its biological effect when it binds to PAC1, VPAC1 and VPAC2 receptors, which are G-protein-coupled receptors.<sup>17</sup> Importantly, infusion of PACAP-38 in migraineurs induces delayed migraine-like headaches that indicate a parallel and possibly synergistic pathway in migraine pathophysiology.<sup>18</sup>

## Role of Serotonin (5 HT) in Migraine

Serotonin is a monoamine neurotransmitter and hormone also known as 5-Hydroxytryptamine (5-HT). Due to its extreme heterogeneity, 5-HT has been classified into seven families. All of them are G-protein coupled receptors except 5-HT<sub>3</sub>, which is a ligand-gated ion channel.<sup>19</sup> Between migraine episodes, serotonin levels often drop, potentially disrupting the serotonin-mediated pain inhibition pathway.<sup>20</sup> This disruption can activate the trigeminal system, leading to worsening of migraine symptoms. It is believed that subtypes of 5-HT receptors may play different functions in migraine. Some receptors, such as 5-HT<sub>1C</sub>, may trigger migraine, while others may reduce it (e.g., 5-HT<sub>1D</sub>).<sup>21</sup>

## Conventional Pharmacological Approaches for Migraine

For decades, conventional therapies have been the primary method for the treatment of migraine, focusing on reducing the pain, decreasing the attack duration, and preventing recurrence. These treatments can be classified into abortive (acute) and prophylactic (preventive) therapies. Abortive and prophylactic therapies serve different roles in the management of migraines.<sup>22</sup> Table 1 outlines conventional treatment approaches for migraine, including examples with their effects, benefits, and limitations.

## Liposomal Opportunity: A Strategic Intervention

Conventional treatments of migraine, such as oral triptans, NSAIDs, and ergot derivatives, are not as effective as they have low therapeutic efficiency due to systemic side effects, poor bioavailability, and limited brain penetration. The Blood-Brain Barrier (BBB) poses a major challenge for delivering drugs effectively to the central nervous system. Tight junctions and active efflux transporters restrict the passage of many therapeutic agents.<sup>40</sup> Liposomes have emerged as a promising carrier to overcome these obstacles due to their physicochemical and biophysical properties.<sup>41</sup> Liposomes are spherical vesicles having an aqueous core encircled by one or more bilayers of phospholipid, which allows the loading of both hydrophilic and lipophilic medications at the same time.<sup>42</sup> Since their development in the 1960s, Liposomes have served as highly effective drug carriers because of their unique capacity to protect encapsulated therapeutics from degradation within the body's physiological environment. This protective feature significantly prolongs the circulation time of the drug and allows for more controlled and sustained release.<sup>43</sup> Figure 3 illustrates a schematic representation of Liposomal Drug Delivery across

the Blood-Brain Barrier for Migraine treatment. Liposomal drug delivery across the BBB in migraine occurs via receptor-mediated transcytosis, adsorptive-mediated transcytosis, and carrier-mediated transport. Receptor-mediated transcytosis involves ligand-functionalised liposomes (e.g., transferrin) binding specific receptors on brain endothelial cells, facilitating their transport across the BBB. Adsorptive-mediated transcytosis is driven by electrostatic interaction between positively charged nanocarriers and negatively charged endothelial membranes, promoting nonspecific uptake. Carrier-mediated transport utilises an endogenous transport protein to facilitate drug entry into the brain.<sup>44</sup>

Liposomes can be categorised on factors such as their size, number of lipid bilayers, and composition. Table 2 presents a classification of liposomes based on their compositions and applications. A clear understanding of these characteristics is essential when choosing the most suitable route of administration and its pharmacokinetic profile.<sup>45</sup> Among these features, the number of bilayers plays an important role, as it influences several key aspects, including encapsulation efficiency, the addition of surface-bound ligands, the rate and pattern of drug release and stability during storage. Furthermore, it affects how liposomes interact with cells, influencing processes such as cellular adhesion, membrane fusion, and internalisation, all of which are critical for achieving effective drug delivery.<sup>46</sup>

Liposomes are classified into four main types based on their average size and lamellarity: Unilamellar Vesicles (ULVs), consisting of a single lipid bilayer surrounding an aqueous core, are commonly divided into size-based categories. Small unilamellar vesicles (SUVs, 20-100nm) are preferred for therapeutic applications due to their prolonged circulation time and passive targeting capability at diseased sites.<sup>47</sup> Large unilamellar vesicles (LUVs,

>100 nm) offer a large aqueous core, making them more suitable for encapsulating hydrophilic agents and small molecules.<sup>48</sup> At the larger end of the spectrum, giant unilamellar vesicles (GUVs, >1000 nm) serve as valuable cell-sized model systems that are useful for understanding the interactions between proteins and lipids.<sup>49</sup>

In contrast, multilamellar vesicles (MLVs, >500 nm) comprise multiple concentric lipid bilayers, resembling an onion-like structure. One of their primary benefits is their stability and ease of preparation. MLVs are suitable for loading the hydrophobic drugs. However, the volume available for drug loading is limited due to the presence of multiple concentric lipid bilayers, which reduce the internal space. Additionally, their large size restricts their use in injectable applications.<sup>50</sup> Bridging the gap between ULVs and MLVs are oligolamellar vesicles (OLVs, 100-1000 nm), which contain 2 to 5 bilayers and provide a balance between drug loading and manageable size.<sup>51</sup> Lastly, multivesicular vesicles (MVs, >1000 nm) consist of multiple non-concentric vesicles encapsulated within a single outer membrane. Their complex internal structure supports high drug encapsulation capacity, extended sustained drug release, low drug leakage rate, combination administration, and several delivery routes.<sup>52</sup>

### Preclinical and Experimental Liposomal Strategies for Migraine Management.

Liposomes have emerged as potential carriers in migraine treatment, with several recent studies exploring their use in enhancing drug delivery to the brain. From intranasal gels to chitosan-coated vesicles, these innovations represent a significant advancement in both acute and preventive treatment strategies. Table 3 summarises recent liposomal formulations for migraine treatment, including preparation methods, routes of administration, and therapeutic outcomes.

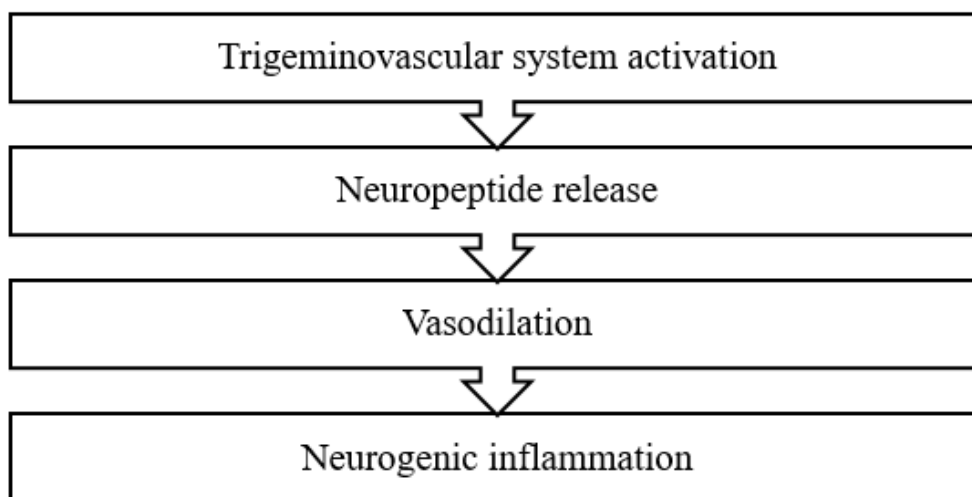


**Figure 1:** Illustrating the involvement of the Trigemino-vascular system in migraine.

**Table 1:** Showing the conventional approaches for migraine treatment, including examples along with their effects, benefits, and limitations.

| Classes                   | Mechanism                                                                                      | Benefits                                                          | Limitations                                                | References |
|---------------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------------------------------------|------------|
| NSAIDs                    | Inhibit COX enzymes → ↓ Prostaglandin synthesis                                                | Effective mild to moderate attacks; inexpensive                   | GI irritation, not effective in severe attacks             | 23         |
| Triptans                  | 5-HT <sub>1B/1D</sub> receptor agonist → Vasoconstriction and ↓ neuropeptide release           | Migraine-specific, rapid onset (especially SC)                    | Contraindicated in CVD, pregnancy, and hemiplegic migraine | 24,25      |
| Ergot Derivatives         | Partial agonist at 5-HT, dopamine, α-adrenergic receptors → Vasoconstriction                   | Long duration of action; effective for prolonged attacks          | Complex side effects, contraindicated in vascular disease  | 26,27      |
| Antiemetics               | Dopamine D <sub>2</sub> receptor antagonist                                                    | Relieves nausea and vomiting; can be used with triptans or NSAIDs | Extrapyramidal side effects                                | 28,29      |
| Gepants                   | CGRP receptor antagonist                                                                       | Oral disintegrating forms available; no vasoconstriction          | Limited long-term data; high cost                          | 30,31      |
| Beta-Blockers             | Competitive inhibitors of β-receptors (β <sub>1</sub> -selectivity and partial agonist action) | Effective in prophylaxis                                          | Fatigue, contraindicated in asthma/diabetes                | 32,33      |
| Antiepileptics            | Modulate voltage channels, ↑ GABA, ↓ glutamate                                                 | Effective in migraine prophylaxis                                 | tremor, fatigue, nausea, and weight gain                   | 34,35      |
| Tricyclic Antidepressants | Inhibit serotonin reuptake                                                                     | Helpful in insomnia or depression comorbidity                     | Sedation, anticholinergic effects                          | 36,37      |
| CGRP mAbs                 | Block the CGRP ligand or receptor                                                              | Monthly/quarterly dosing; migraine-specific                       | High cost, limited access                                  | 38,39      |

## The Role of CGRP and the Trigeminal System in Migraine

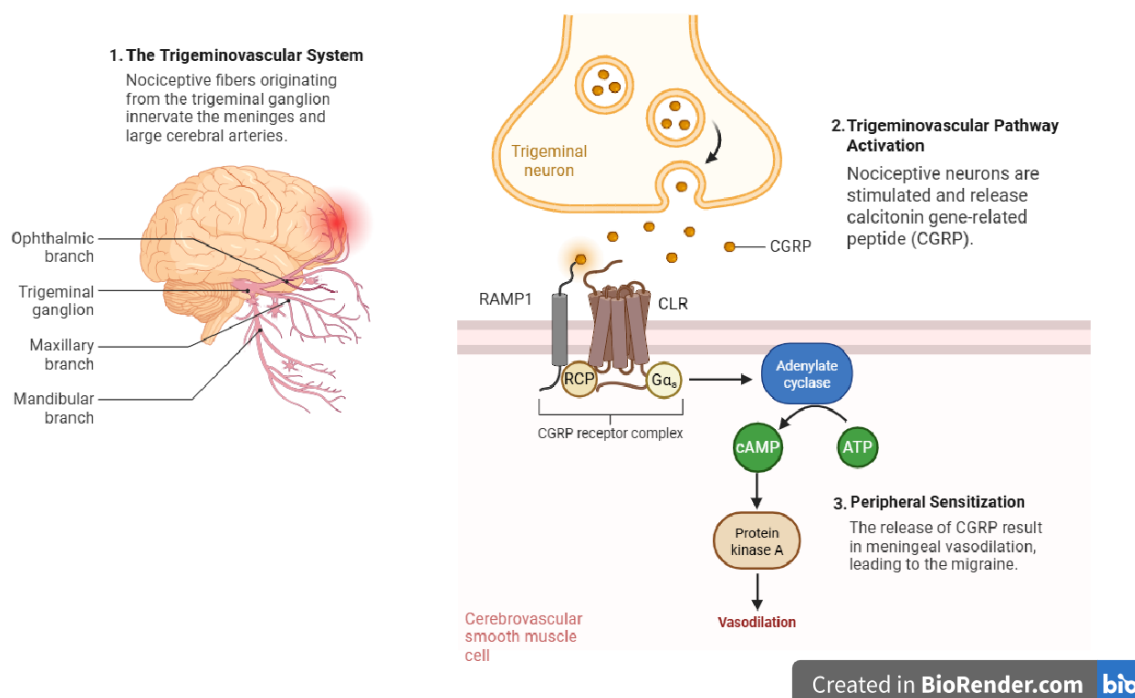
**Figure 2:** Illustrating the involvement of CGRP and Trigeminal system.

**Table 2: Classification of liposomes based on their compositions and applications.**

| Type                          | Description                                                                                                                                                                                                                                                                           | Relevance in Migraine Therapy                                                                                                                                                       | References |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Conventional Liposomes        | These liposomes are produced using either natural or synthetic phospholipids with or without cholesterol. The addition of cholesterol altered the liposomes' fluidity, stability, and rigidity.                                                                                       | Entrap hydrophilic compounds. Stabilise compounds, thus avoiding early degradation in the systemic circulation.                                                                     | 53         |
| PEGylated (Stealth) Liposomes | Sterically stabilised liposomes are created by coating their surfaces with a small amount of biologically inert polymer, forming a protective layer that enhances their stability.                                                                                                    | Show extended circulation time, resulting in improved accumulation.                                                                                                                 | 54         |
| Targeted Liposomes            | These liposomes are engineered with targeting ligands such as cell-penetrating peptides, antibodies, or naturally occurring molecules like transferrin and glutathione, that can recognise receptors on brain endothelial cells and facilitate transport via the blood-brain barrier. | Targeted liposomal delivery improves drug transport to the brain by directing the formulation to the desired site, which boosts therapeutic efficacy while minimising side effects. | 55         |
| Charged Liposomes             | Charged liposomes have a surface charge and are often classified as cationic or anionic.                                                                                                                                                                                              | Because of their capacity to repel each other and decrease aggregation, charged liposomes showed enhanced liposomal stability during storage.                                       | 56         |
| Stimuli-responsive Liposomes  | Stimuli-responsive liposomes are designed to release their drug in response to physicochemical or biochemical stimuli, such as temperature or pH.                                                                                                                                     | Enable controlled drug release, enhanced intracellular distribution.                                                                                                                | 57         |

### Safety and Toxicity of Liposomal Drug Delivery

Liposomes are generally considered biocompatible and safe because they are composed of naturally occurring phospholipids; however, specific safety concerns arise when used for migraine therapy. The presence of the BBB requires surface-modified liposomes, which may alter their biological interactions and toxicity profile. Rapid clearance by the Reticuloendothelial System (RES) can decrease drug availability, while PEGylation prolongs circulation time but may cause hypersensitivity and immune reactions. Cationic liposomes might also increase cytotoxicity due to interactions with neuronal and endothelial membranes.<sup>67</sup>

For intranasal delivery, it is important to assess local safety concerns such as nasal mucosal irritation, ciliotoxicity, and long-term effects on the olfactory epithelium. Additionally, the buildup of liposomal components in brain tissue and possible neurotoxicity needs thorough investigation. Therefore, a comprehensive safety assessment is crucial to ensure the safe clinical use of liposomal drug delivery systems in migraine treatment.<sup>68</sup>

### Future perspective

Although liposomal drug delivery systems show significant potential in preclinical models for migraine therapy, their translation into clinical practice remains a challenge. Future

studies should focus on well-designed, large-scale randomised clinical trials to thoroughly evaluate the safety, efficacy, and pharmacokinetic profiles of liposome-based formulations in humans. Additionally, the development of ligand-functionalised and stimuli-responsive liposomal systems offers enhanced specificity and therapeutic efficacy. Intranasal delivery strategies also require further optimisation to improve drug absorption, residence time, and patient compliance.<sup>69</sup> Furthermore, combination therapy approaches that are co-encapsulated with anti-inflammatory, neuroprotective, or CGRP-modulating agents within a single liposomal system may offer synergistic benefits, including improved pharmacokinetics and enhanced clinical efficacy.<sup>70</sup>

From a regulatory perspective, the transition of liposomal formulations from laboratory to clinical application necessitates strict adherence to quality and safety standards. Critical Quality Attributes (CQAs), including particle size, polydispersity index, zeta potential, encapsulation efficiency, and *in vitro* release profile, must be carefully controlled to ensure uniformity and reproducibility. Additionally, scale-up challenges, storage stability, safety, and clinical validation must be addressed. Manufacturing in accordance with Good Manufacturing Practices (GMP) is essential to ensure quality, safety, and regulatory compliance.<sup>71</sup>

**Table 3: Summary of recent liposomal formulations for migraine treatment, including preparation methods, routes of administration, and therapeutic outcomes.**

| Sl. No. | Formulation                                                                              | Method of preparation                                                                                                   | Route of administration | Outcome                                                                                                                                                                                               | References |
|---------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 1.      | Sumatriptan chitosan loaded                                                              | Prepared using the thin film hydration and extrusion method.                                                            | Nasal route             | Chitosan coating enhances stability and mucoadhesion by modifying surface charge.                                                                                                                     | 58         |
| 2.      | Zolmitriptan (liposomal gel)                                                             | Optimised by central composite design (CCD), the Conventional rotary melting sonication method was used.                | Nasal route             | Zolmitriptan Liposomal gel enhances the drug absorption and effectiveness.                                                                                                                            | 59         |
| 3.      | Liposomal Curcumin with sumatriptan                                                      | Film hydration method.                                                                                                  | Intravenous             | Results show improved antioxidant effect and enhanced pain control.                                                                                                                                   | 60         |
| 4.      | Liposomal Epigallocatechin gallate co-administration with Metoclopramide hydrochloride   | Film hydration method.                                                                                                  | Intraperitoneal (rats)  | Liposomal EGCG with metoclopramide demonstrates greater anti-nociceptive and antioxidant advantages in migraine therapy.                                                                              | 61         |
| 5.      | Liposomal curcumin with naproxen                                                         | Film hydration method.                                                                                                  | Intravenous             | Enhanced both analgesic and antioxidant effects in the rat model of Migraine.                                                                                                                         | 62         |
| 6.      | Poloxamer 407-based intranasal thermoreversible gel of zolmitriptan-loaded nanoethosomes | For optimisation, a 3 <sup>2</sup> factorial design was used, and the Ethanol injection method was employed.            | Intranasal              | The study found that formulations G3 and G6 exhibited sustained release, efficient nasal gelation, and effective drug permeation.                                                                     | 63         |
| 7.      | Flexible liposome embedded <i>in situ</i> Thermoreversible gel of Rizatriptan Benzoate   | A 3 <sup>2</sup> Full Factorial design was used for optimisation, and the Ethanol injection sonication method was used. | Intranasal              | The study concluded that formulation F2 showed enhanced nasal drug permeation, improved bioavailability, and showed no evidence of tissue damage, making it a safe and effective option for migraine. | 64         |
| 8.      | Thermosensitive <i>in situ</i> Nasal Hydrogel of Sumatriptan Succinate                   | Optimised by a 3 <sup>2</sup> factorial design and formulated by the Thin-film hydration method.                        | Intranasal              | The formulation improved nose-to-brain transport, indicating its potential as an effective non-invasive migraine therapy.                                                                             | 65         |

| Sl. No. | Formulation                      | Method of preparation                                                                          | Route of administration | Outcome                                                                                           | References |
|---------|----------------------------------|------------------------------------------------------------------------------------------------|-------------------------|---------------------------------------------------------------------------------------------------|------------|
| 9.      | Propranolol HCL-Loaded Liposomes | Prepared by the thin-layer hydration process and optimised by the Design of Experiments (DOE). | Intranasal              | The liposomal formulation demonstrates potential for intranasal delivery in migraine prophylaxis. | 66         |

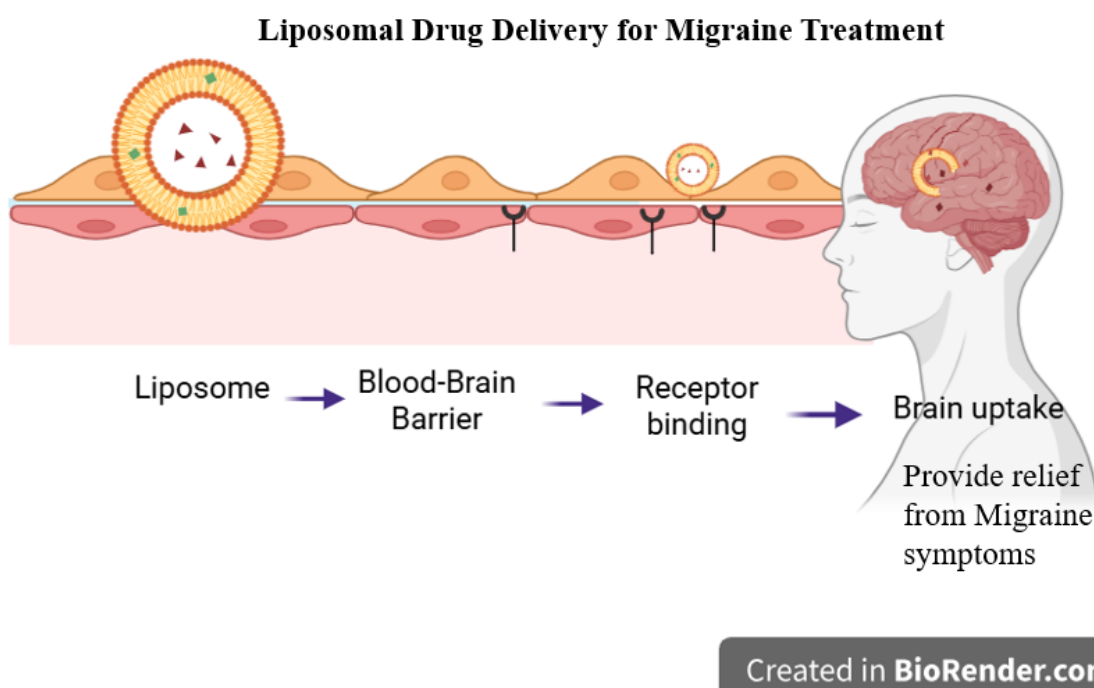


**Figure 3:** Schematic representation of Liposomal Drug Delivery across the Blood-Brain Barrier for Migraine treatment.

## CONCLUSION

Migraine is a widespread and often disabling neurological condition that profoundly impacts the quality of life and capabilities of people. Conventional pharmacological treatments such as NSAIDs, triptans, and ergot derivatives can provide symptomatic relief, but have poor bioavailability, limited brain penetration, systemic side effects, and inconsistent therapeutic efficacy. These challenges require novel strategies to enhance drug delivery and therapeutic effects in migraine management. Liposomes have emerged as a potential nanocarrier system capable of overcoming various barriers associated with traditional drug delivery. Their unique structural properties, such as amphiphilic nature, biocompatibility, and tendency to encapsulate both hydrophilic and lipophilic drugs, enable enhanced drug stability, sustained release, and targeted delivery, especially across the blood-brain barrier. Liposomal formulations, particularly when administered via intranasal, intravenous, or transdermal routes, have demonstrated remarkable advancements in preclinical

models in terms of increasing brain uptake, extending drug release, and reducing peripheral side effects. Recent preclinical studies on the liposomal delivery of antimigraine drugs such as sumatriptan, zolmitriptan, curcumin, propranolol, and natural antioxidants have shown substantial improvement in both acute and preventive therapy. Compared with traditional formulations, these studies have shown better pharmacokinetics, greater therapeutic effectiveness, and superior patient safety profiles. Despite encouraging outcomes, clinical translation of liposomal therapies remains limited. The goal of future research must be to close the gap between the bench and the bedside through standardised regulations, scalable production techniques, and well-planned clinical trials. Additionally, including multifunctional and stimuli-responsive liposomes and investigating patient-specific strategies may greatly improve the therapeutic environment. In summary, liposomes are a highly inventive and strategic drug delivery platform for the treatment of migraines, providing a game-changing method that may

overcome the long-standing drawbacks of existing treatments and greatly enhance patient results.

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## ABBREVIATIONS

**CGRP:** Calcitonin gene-related peptide; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **BBB:** Blood-brain barrier; **TCC:** Trigemino-cervical complex; **PACAP:** Pituitary adenylate cyclase-activating polypeptide; **CLR:** Calcitonin receptor-like receptor; **RAMP1:** Receptor activity-modifying protein 1; **cAMP:** cyclic adenosine monophosphate; **PKA:** Protein kinase A; **SP:** Substance P; **TAC:** Tachykinin; **NKRs:** Neurokinin receptors; **5-HT:** 5-hydroxytryptamine; **EPR:** Enhanced permeability and retention; **ULVs:** Unilamellar vesicles; **SUVs:** Small unilamellar vesicles; **LUVs:** Large unilamellar vesicles; **GUVs:** Giant unilamellar vesicles; **MLVs:** Multilamellar vesicles; **MVVs:** Multivesicular vesicles; **EGCG:** Epigallocatechin gallate; **CCD:** Central composite design; **DOE:** Design of experiments; **COAs:** Critical Quality Attributes; **GMP:** Good Manufacturing Practices; **RES:** Reticuloendothelial system.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## SUMMARY

This review examines the growing significance of liposomal drug delivery systems in managing migraines, drawing attention to their advantages over more conventional therapies like NSAIDs, triptans, and ergot alkaloids. Conventional therapies frequently face limitations such as poor brain penetration, systemic side effects, and low bioavailability. In contrast, liposomes, spherical vesicles capable of encapsulating both hydrophilic and lipophilic drugs, offer a strategic alternative for targeted brain delivery. The article outlines the complex pathophysiology of migraine, highlighting the role of the trigeminovascular system, neuropeptides, serotonin, and their interaction in migraine onset and progression.

Several types of liposomes are explored, including conventional, PEGylated, targeted, and stimuli-responsive systems. The review draws attention to their design, size, lamellarity, and delivery route. Preclinical studies involving sumatriptan, zolmitriptan, propranolol, curcumin, and natural antioxidants via intranasal and intravenous routes have demonstrated increased bioavailability, brain uptake, and therapeutic efficacy. However, despite promising results from preclinical studies, the path to clinical

application remains challenging. Future research should focus on clinical trials, regulatory pathways, scalable manufacturing, and the development of multifunctional and patient-specific liposomal systems. Ultimately, liposomal technology holds the potential to revolutionise migraine treatment by offering a safer, more efficient, and precisely targeted therapeutic option for both immediate relief and long-term prevention.

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