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Nanoformulation innovations: Revolutionizing precision in migraine therapy

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ABSTRACT

Objective(s): Migraine, a serious neurological disease that affects millions of people worldwide, is one of the most considerable burdens on the healthcare system and has significant economic implications. Even though various treatment methods are available, including medication, lifestyle changes, and behavioral therapy, many migraine sufferers do not receive adequate relief or experience intolerable side effects. Hence, the present review aims to evaluate the nanoformulation regarding migraine therapy.

Materials and Methods: Between 2005 and 2024, specific keywords were used to search several databases, such as Pubmed, Google Scholar, and Scopus.

Results: The nanoformulation field is an increasing field within nanotechnology that offers new solutions for treating migraine, including improving drug delivery, increasing therapeutic efficacy, and minimizing side effects. By combining nanoscale materials with therapeutic agents, nanoformulations can enhance bioavailability, sustain drug release, deliver targeted drugs, and penetrate the Blood-Brain Barrier (BBB) more efficiently. Nanoformulation has the potential to be a useful tool for migraine therapy. However, several challenges still need to be overcome, such as the BBB penetration, safety and biocompatibility of the product, manufacturing, and scalability reproducibility to pass regulatory approval and affordability. To overcome these challenges, research efforts should be focused on developing innovative techniques to penetrate the BBB, target specific migraine pathways, incorporate personalized medicine approaches, and develop nanotechnology-based diagnostics.

Conclusion: A nanotechnology-based approach aims to revolutionize migraine therapy, improving patient outcomes and living standards by offering personalized and precise treatments.

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Introduction

Migraine is a serious neurological disease that causes weakening episodes of severe vomiting and headaches, accompanied by nausea and a sensitivity to light and sounds (1). There are approximately 1 billion people around the world affected by migraine, making it one of the most widespread and disabling conditions in the world (2). Despite the significant impact migraine has on a person's quality of life and productivity in the workplace, migraine remains an ununderstood and undertreated condition. There are a variety of neurobiological, genetic, and environmental factors that contribute to migraine's pathophysiology (3). It is widely believed that abnormal neuronal excitability and a malfunction in pain processing pathways in the brain cause migraine. In migraine attacks, several neurotransmitters influence the development and proliferation, including dopamine, serotonin, and Calcitonin Gene-Related Peptide (CGRP) (4). The severity and frequency of migraine attacks have been reduced over time by a variety of treatment modalities.

There are several drugs available to treat migraine, such as triptans, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), ergot alkaloids, as well as preventive medication such as Antiepileptic Drugs (AEDs), beta-blockers, and antidepressants (5). Moreover, stress management techniques, complementary therapies like biofeedback, acupuncture, and lifestyle modifications have been advocated for the treatment of migraine (6). Even though there are many treatment options available to migraine sufferers, many of them still experience inadequate relief from their migraine or experience intolerable side effects as a result of conventional treatments (7). Long-term use of certain migraine medications can also cause rebound headaches, drug resistance, and other side effects, so alternative migraine management approaches are essential (8). Recently, interest has increased in developing novel drug delivery systems to improve migraine treatment safety, compliance, and efficacy (9).

Nanotechnology-based formulation has emerged as a promising candidate for targeted drug delivery to migraine

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patients' Central Nervous Systems (CNS) (10). Using nanoformulations in drug delivery can revolutionize the treatment of migraine by leveraging the impressive properties of nanoscale materials (11). Nanotechnology involves manipulating particles smaller than 100 nanometers, a scale at which materials exhibit distinct interactions and behaviors with living organisms (12). Using nanocarriers as sophisticated vehicles to encapsulate therapeutic agents enables agents to be shielded from degradation, facilitates their targeted delivery to specific anatomical sites in the body, and ensures that they reach the desired locations (13). A significant advantage of nanoformulations is that they can overcome traditional drug delivery systems' inherent limitations. As a result of oral and parenteral administration routes, drug bioavailability is often poor, clearance from the circulation is rapid, and off-target effects are frequent, resulting in frequent dose administrations to achieve therapeutic concentrations at the intended site of action (14). In contrast, nanocarriers can enhance drug stability, prolong drug release kinetics, and enhance tissue penetration, thus improving therapeutic efficacy while minimizing systemic toxicity (15). Moreover, nanoformulations can modulate drug biodistribution profiles and pharmacokinetics with unparalleled versatility (16).

Researchers can tailor the behavior of Nanoparticles (NPs) in biological environments by adjusting their physicochemical properties, such as their surface charge, size, surface chemistry, and shape (17, 18). By controlling physicochemical properties, the design of nanocarriers can optimize pharmacokinetic profiles, leading to sustained drug release over long periods, less frequent dosing, and improved therapy compliance. (19). Migraine therapy relies heavily on nanocarriers' ability to cross physiological barriers, such as the Blood-Brain Barrier (BBB) (20). Many migraine medications are ineffective due to the BBB, which prevents therapeutics from reaching the CNS. Nevertheless, nanocarriers have the potential to bypass the BBB altogether or exploit endogenous transport mechanisms, thus providing targeted delivery of drugs to the brain parenchyma (21). The targeted delivery method promotes drug accumulation at the pathological site while minimizing systemic exposure, reducing systemic adverse effects (22).

Researchers can harness nanotechnology's power to develop precision, productive approaches to migraine management. The present review aims to overview the current migraine treatment landscape and the challenges and potential benefits of nanoformulation approaches. The discussion will focus on the efficacy and safety of nanoformulated migraine treatments and the various nanocarriers and delivery strategies used to deliver targeted drugs to the CNS. The final objective will be to improve the quality of life and patient outcomes by applying nanotechnology to migraine management.

Methodology

Between 2005 and 2024, we conducted a comprehensive literature review using specific keywords, including "nanoformulation," "precision therapy," "migraine treatment," "drug delivery," and "nanomedicine." The primary databases consulted were PubMed, Google Scholar, and Scopus. These sources were chosen for their extensive and reputable scientific content. Relevant studies, reviews, and clinical trials were meticulously selected and analyzed to gather data on the advancements and applications of nanoformulations in precision migraine therapy. The collected information was synthesized to provide a comprehensive overview of current innovations and prospects in the field.

Overview of migraine

Migraine is a multifaceted neurological disease. There are approximately 1 billion people who suffer from the disease worldwide, making it a prevalent and disabling condition. Despite migraine's widespread impact, researchers and clinicians still struggle to understand its pathophysiology, etiology, and best management strategies (23). Symptoms of migraine include severe headaches accompanied by nausea, vomiting, photophobia, and phonophobia (24). The migraine manifests in different ways and exhibits considerable variability in symptoms, duration, and severity over time. Migraine are episodic headaches characterized by recurrent headache episodes separated by intervals of symptom-free time between attacks (25). It is common for migraine attacks to range in severity and frequency from occasional mild headaches to frequent, debilitating attacks that significantly compromise daily life (26).

There are several factors associated with migraine pathogenesis, including neurobiological, genetic, and environmental factors that contribute to the development of migraine symptoms (27). Researchers have found that migraine is associated with abnormalities of the peripheral and CNS as well as altered neurovascular function, cortical excitability, and neurotransmitter signaling (28). Migraine attacks are initiated, propagated, and modulated by these aberrations, which ultimately result in the patient's characteristic symptoms (29). The pathophysiology of migraine often involves Cortical Spreading Depression (CSD), characterized by a transient period of neuronal hyperactivity followed by a period of neuronal depression (30). There are a variety of subtypes, such as chronic migraines, migraine with aura, and migraine without aura. The International Classification of Headache Disorders (ICHD) covers migraine subtypes. Various migraine attack characteristics, including preceding aura symptoms, duration, intensity, and frequency, are used to diagnose migraine attacks (31). A migraine treatment strategy has the purpose of improving acute migraine symptoms, preventing migraine attacks, and improving the overall quality of life of patients with migraine. There are several acute treatment options available, including analgesics such as ergot alkaloids, NSAIDs, and triptans, which target the pain pathways behind migraine headaches as well as the vascular mechanisms that contribute to them (32).

Migraineurs experiencing the aura phase, which includes reversible neurological symptoms like sensory disturbances, visual disturbances, and motor deficits, are believed to harbor CSD. Although the exact mechanisms triggering headache pain associated with CSD remain unclear, they may involve activating trigeminal nociceptive pathways and releasing pro-inflammatory mediators (33). Additionally, the pathogenesis of migraine has been thought to be related to abnormal regulation of neurotransmitter systems, such as dopamine, CGRP, and serotonin (34).

A disruption of serotonin receptor function is thought to contribute to migraine susceptibility, with serotonin being a critical factor in modulating neuroinflammation, pain perception, and vascular tone (35). Additionally, dysfunctions in the CGRP and dopaminergic signaling pathways have been linked to progression and migraine onset, highlighting the complex interactions between neurotransmitter systems (36). Migraine is also strongly affected by genetic predisposition, with heritability estimates and familial clustering suggesting a vital genetic

component. Many genetic variants have been identified as being linked to migraine risk by Genome-Wide Association Studies (GWAS), most of which are associated with synaptic transmission, neuronal excitability, and ion channel function. However, migraine is a highly complex disease with a highly complex genetic architecture (37). Multiple genetic loci are implicated in the disease's susceptibility and the phenotype's variability. Besides genetic factors, environmental triggers and lifestyle factors may also play a part in precipitating migraine attacks or causing them to become worse (38).

The most common triggers are weather changes, hormonal fluctuations, stress, alcohol consumption, sleep disturbances, sensory stimuli (such as loud noises, strong odors, and bright lights), environmental toxins, and caffeine consumption (39). Although there is no clear understanding of the mechanisms involved in triggering migraine attacks, it is believed that triggers modify vascular tone, neuronal excitability, neuroinflammatory responses, and ultimately resulting in triggering or exacerbating migraine-related symptoms. Due to the lack of specific biomarkers and diagnostic tests that can be used to diagnose migraine, clinical diagnosis still needs to be improved due to the reliance on patient reports of their medical history and symptoms (40).

As another treatment option, migraine patients may be prescribed antiemetic medications to reduce vomiting and nausea caused by migraine attacks. As a result, acute migraine treatments often lack efficacy and tolerability, as well as their potential to cause Medication Overuse Headaches (MOH), which calls for alternative approaches to migraine management (41). Migraine treatment has recently undergone a revolution with the advent of targeted migraine therapies, such as monoclonal antibodies that target CGRP or its receptors, which provide more effective and specific treatments for both preventive and acute migraine (42). As compared with conventional pharmacological treatments, biologic agents have the potential to reduce migraine attacks' severity and frequency, improving outcomes and minimizing adverse effects (43). Furthermore, non-pharmacological treatments for migraine, such as lifestyle modification, behavioral therapy, and neuromodulation, provide additional options for personalized treatment (44). Patients who undergo migraine can find treatment modalities available, but many still experience poor relief, refractoriness to treatment, or intolerable side effects, which calls for innovative approaches to treat migraine (45). As nanotechnology-based drug delivery systems become more prevalent in recent years, nanoformulations show great potential for improving migraine therapies' efficacy, safety, and adherence. In the future, nanoformulations can overcome the limitations of conventional drug delivery systems by encapsulating therapeutic agents in nanocarriers and optimizing their physicochemical properties. Nanoformulations can improve migraine medications' targeted delivery to the CNS, enabling them to exert their therapeutic effects more precisely and efficiently (46, 47).

Current treatment options for migraine and their limitations

Despite being a weakening neurological disease, migraine presents significant challenges for healthcare providers and patients because of their complex heterogeneous and pathophysiology clinical presentations. Various treatments can reduce migraine symptoms and minimize their severity and frequency (Figure 1), but they are often limited in their adverse effects, efficacy, and tolerability.

Acute treatment options

Nonsteroidal anti-inflammatory drugs

Aspirin, naproxen, and ibuprofen are commonly used as NSAIDs to treat acute migraine pain by reducing inflammation and suppressing prostaglandin synthesis (48). Some migraine sufferers have found relief through the use of NSAIDs. However, their efficacy may be limited when the migraine is severe or refractory, and prolonged treatment may result in gastrointestinal adverse effects such as bleeding and ulcers (49).

Triptans

In particular, triptans are a group of medications that target migraine symptoms by attaching themselves to the

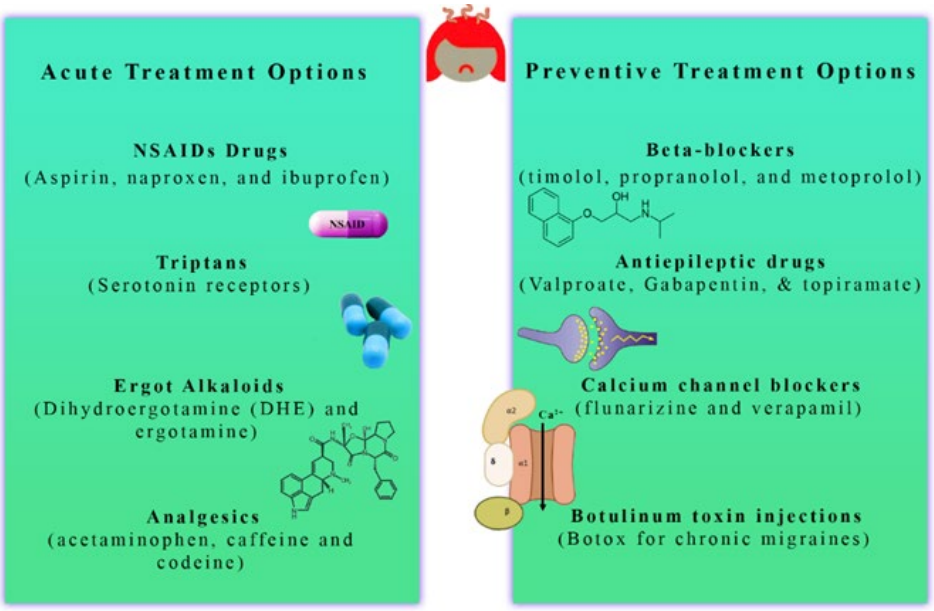

Figure 1. Current treatment options for migraine

receptors of serotonin in the brain and constricting the blood vessels that are dilated (50). Migraine attacks can be effectively prevented, and symptoms such as photophobia and nausea are alleviated with triptans (51). However, the use of triptans is limited by the possibility of cardiovascular problems such as stroke, coronary artery spasm, and myocardial infarction, particularly in those who have preexisting cardiovascular issues.

Ergot alkaloids

Acute migraine attacks have been treated for decades with ergot derivatives such as Dihydroergotamine (DHE) and ergotamine (52). Several medications can increase serotonin levels and inhibit the release of vasoactive peptides, but they exert their effects differently (53). Ergot alkaloids have been proven to be effective in averting migraine attacks, but they can cause significant side effects, including nausea, vasoconstriction of peripheral vessels, and vomiting.

Analgesics

In mild to moderate migraine pain, Over-The-Counter (OTC) analgesics such as acetaminophen and combinations of acetaminophen and caffeine or codeine may relieve symptoms (54). The efficacy of OTC analgesics in treating migraine attacks that are severe or persistent is limited, and long-term use may become associated with rebound headaches and MOH (55).

Calcitonin gene-related peptide-targeting drugs for migraine

Calcitonin gene-related peptide (CGRP) has emerged as a pivotal target in migraine therapeutics, leading to the development of CGRP inhibitors as promising treatments (56). Understanding the pharmacology of these drugs is crucial for informed treatment decisions. CGRP inhibitors, including monoclonal antibodies and small molecule antagonists, act by blocking the CGRP pathway, thereby reducing the frequency and severity of migraine attacks (57). Their efficacy in clinical trials underscores their potential as a novel therapeutic approach for migraine management (58). However, despite their promise, CGRP inhibitors may pose potential off-target effects, including cardiovascular risks and liver toxicity, necessitating careful patient selection and monitoring (59). Moreover, ongoing research is shedding light on the broader implications of CGRP in migraine pathophysiology, suggesting potential future directions for therapy (60). While CGRP inhibitors represent a significant advancement in migraine treatment, clinicians must weigh their benefits against potential risks and consider individual patient factors to optimize therapeutic outcomes and ensure patient safety (61, 62).

Preventive treatment options

Beta-blockers

A beta-blocker, such as timolol, propranolol, and metoprolol, is commonly prescribed as a first-line migraine preventive medication because it reduces neuronal excitability and inhibits sympathetic nervous system activity (63). In addition to reducing migraine severity and frequency, beta-blockers may also cause depression, cardiovascular adverse effects, and fatigue, which may limit their use (64).

Antiepileptic drugs

Valproate, gabapentin, and topiramate are AEDs that modulate neurotransmitter release, inhibit cortical hyperexcitability, and stabilize neuronal membranes to prevent migraine attacks (56, 57). However, adverse effects associated with AEDs can impact the central nervous system (CNS), leading to mood disturbances, cognitive impairment, and dizziness, which can limit long-term adherence and tolerability (65).

Calcium channel blockers

Several calcium channel blockers, such as flunarizine and verapamil, have been investigated to determine if they may prevent migraine headaches by modulating the release of neurotransmitters and preventing calcium from entering neurons (66, 67). In addition to reducing migraine severity and frequency, calcium channel blockers may cause adverse cardiovascular effects such as peripheral edema, hypotension, and bradycardia (68, 69).

Botulinum toxin injections

It has been suggested that Botulinum toxin type A (Botox) injections can be used as a treatment option for chronic migraine, which is defined as migraine occurring 15 days or more a month (70). The effects of Botox are attributed to the inhibition of the release of neurotransmitters involved in the transmission of pain, as well as the reduction of peripheral sensitization and muscle hyperactivity (71). A Botox injection can significantly reduce migraine symptoms for some chronic migraine. However, their effectiveness varies from person to person and must be repeated every 12 weeks (72).

New drugs

The newest drugs for the acute treatment of migraine include Zavzpret (zavegepant) nasal spray, approved in March 2023, and Nurtec ODT (rimegepant) and Ubrelvy (ubrogepant), orally-administered calcitonin gene-related peptide (CGRP) receptor antagonists (gepants), approved in 2020 (73, 74). Additionally, Reyvow (lasmiditan), the first serotonin (5-HT) 1F receptor agonist, offers a novel mechanism for migraine relief. New formulations of older drugs like sumatriptan and rizatriptan, which are serotonin (5-HT) receptor agonists (triptans), have also been approved. For migraine prevention, recent advancements include Qulipta (atogepant), an oral CGRP antagonist approved in September 2021 for episodic migraine, and monoclonal antibody CGRP antagonists such as Aimovig, Ajovy, Emgality, and Vyepti (75-78).

Introduction to nanoformulation

There are various migraine treatment options available, but most migraine patients do not experience adequate relief, treatment refractoriness, or intolerable side effects from the current therapies. Moreover, migraine sufferers frequently have comorbidities, overuse of medications, and varying responses to treatment. As a result, it is essential to develop new therapeutic strategies targeting migraine's underlying pathophysiology while optimizing patient outcomes and minimizing adverse effects (79). Using nanoformulations to overcome these challenges will be discussed in the next section. The development of nanotechnology as a method for drug delivery has emerged as a promising frontier for various medical conditions, including migraine, that currently lack effective treatment modalities (80). In nanotechnology, nanoformulation involves the development of nanoscale drug delivery systems designed to encapsulate, protect, and

deliver therapeutic agents to specific body locations (81). Using the unique physical and chemical characteristics of NPs, researchers are developing migraine medications that will improve therapeutic efficacy, pharmacokinetics, and biodistribution (82). Nanoformulation aims to manipulate particles with sizes ranging from 1 to 100 nanometers, a scale where materials behave differently and interact differently with the body (83, 84). Many materials can be used as nanocarriers, including metals, lipids, inorganic and polymers NPs, each with its benefits regarding stability, drug density, and biocompatibility (85-87). Using nanocarriers as sophisticated delivery vehicles, therapeutic agents can be encapsulated, protected from degradation, and delivered efficiently to cell types or specific tissues (88).

Nanoformulations advantages

Nanoparticles can improve bioavailability by enhancing poorly permeable or soluble drugs' absorption, dissolution rate, and solubility (89). It has been shown that hydrophobic drugs may be encapsulated within lipid-based NPs or conjugated to hydrophilic polymers to overcome the challenges associated with the delivery of hydrophobic drugs and maximize therapeutic effects (90, 91).

Sustained release kinetics

With nanoformulations, drugs can be designed to have sustained release kinetics, prolonging their action and reducing dosing frequency (92). Researchers can modulate the surface properties, size, and shape of NPs to control the rate at which drugs are released and optimize the profile of their pharmacokinetics to achieve extended therapeutic concentrations (93, 94).

Targeted drug delivery

The surface of target cells can be addressed with particular targeting ligands, including aptamers, antibodies, and peptides, or to facilitate specific binding (95, 96). This method can precisely deliver therapeutic agents to diseased tissues or organs with a minimum effect on healthy tissues, improving therapeutic efficacy and minimizing systemic adverse effects (97, 98).

Crossing biological barriers

In addition to the BBB, nanoformulations can penetrate the mucosal epithelium, enabling therapeutics to be delivered to previously inaccessible anatomical sites (99). Pharmacologists can enhance drug penetration into target tissues by engineering NPs with specific physicochemical properties or exploiting endogenous transport mechanisms (100, 101).

Nanoformulation approaches for migraine treatment

The use of nanoformulations in migraine therapy offers a promising means of improving the efficacy and delivery of existing migraine medications while minimizing side effects. Several nano formulation methods have been investigated for migraine treatment (Figure 2), which will be discussed below.

Lipid-based nanocarriers

The potential application of lipid-based NPs in migraine therapy has gained significant attention, including Nanostructured Lipid Carriers (NLCs), liposomes, and Solid Lipid Nanoparticles (SLNs) (102). Nanocarriers can

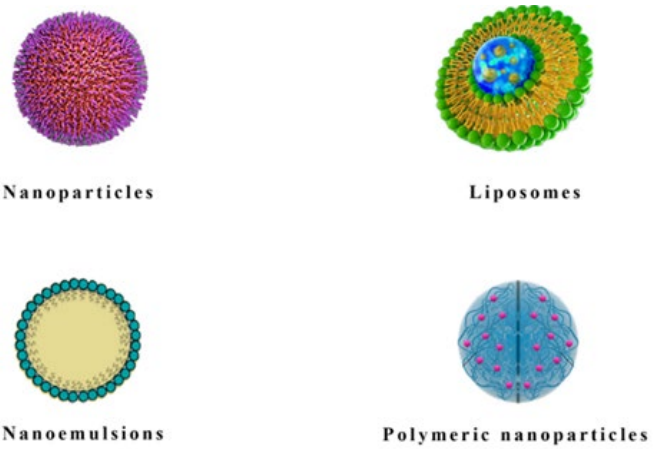

Figure 2. Nanoformulation approaches for migraine treatment

encapsulate a wide range of hydrophilic and hydrophobic drugs, such as trigeminal ganglion antagonists, NSAIDs, and triptans, and deliver them to the brain parenchyma, where they will exert their therapeutic effects (103). As a drug delivery vehicle for migraine treatment, lipid-based nanocarriers have several advantages, including stability, biocompatibility, and combining hydrophilic and lipophilic drugs (104).

Polymeric nanoparticles

The use of polymeric NPs for migraine therapy has been demonstrated as a versatile platform for delivering controlled drug delivery using biodegradable polymers, such as chitosan, Poly Ethylene Glycol (PEG), and Poly Lactic-co-Glycolic Acid (PLGA) (105). A wide range of therapeutic agents can be encapsulated with NPs, protected from degradation, and released over a prolonged period (106). Using polymeric NPs, migraine medications can be designed to target specific cells or tissues in the CNS, such as astrocytes or microglia, that play an important role in migraine pathogenesis (107).

Nanoemulsions

There are certain types of nanoemulsions, for example, the nanoemulsions of oil and water, which surfactants have stabilized to encapsulate hydrophilic or lipophilic drugs inside nanoscale droplets. With nanoemulsions, migraine therapy can be improved through enhanced gastrointestinal absorption, increased drug solubility, and systemic delivery of drugs to the central nervous system (108, 109). Depending on patient preference or clinical consideration, nanoemulsions can be administered orally, intravenously, or intranasally, providing flexibility and tailored treatment approaches (110-112).

Recent studies

Curcumin

A study in 2021 showed there was a significant reduction in migraine attack frequency and serum levels of Interleukin 1 Beta (IL-1β) between individual treatments and the combination of n-3 fatty acids and nano-curcumin (P<0.001) (113). However, after numerous experimental modifications, its importance was lost, and there was a significant reduction in IL-1β gene expression between the combination and individual groups (P<0.05).

A 2019 study conducted to evaluate the combination of

liposomal curcumin and naproxen improved anti-oxidant and anti-nociceptive actions compared to naproxen alone or curcumin solution in rat migraine models, suggesting a promising therapeutic approach (114). Notably, there was a significant reduction in oxidative stress markers and pain between a combination of naproxen (2.8 mg/kg) with liposomal curcumin (2 mg/0.1 kg) and naproxen groups (P<0.001).

Abdolahi *et al.* (2019) conducted a study to examine the association between migraine and recurrent pain attacks with neuroinflammatory processes involving the Cyclooxygenase (COX-2) and Inducible Nitric Oxide Synthase (iNOS) pathways (115). The omega-3 fatty acids and curcumin contain anti-inflammatory properties that target the expression of iNOS/COX-2. An analysis of 74 migraine patients was conducted in the study. There was a significant reduction in iNOS/COX-2 levels and clinical symptoms between omega-3 and nano-curcumin (P<0.05). As a result, the treatment was found to be promising for the prevention of migraine. Table 1 summarizes the studies about curcumin nanoformulations used for migraine.

Zolmitriptan

Zolmitriptan-loaded PLGA NPs have shown a 14.13-fold increase in brain delivery compared to the free drug in animal studies (46). These NPs also significantly reduced hyperalgesia and photophobia in migraine models (Swiss albino mice).

Moreover, a 2017 study showed the low bioavailability of Zolmitriptan (ZMT), which effectively treats migraine (112). Nasal mucoadhesive nanoemulsion formulations have been developed to enhance direct delivery to the brain for high concentrations in the brain and rapid action. An investigation of the viability of ZMT mucoadhesive nanoemulsions was conducted, which included evaluating and preparing drug content, morphology, zeta potential, residence time, particle size, and viability of nasal mucosa permeation. An in vivo study in mice compared its pharmacokinetics in mice with intravenous and nasal solutions, finding that the mucoadhesive nanoemulsion produced an improved brain Area Under the Curve (AUC 0-8) and a lower Time to peak drug concentration (Tmax) due to its more excellent permeability and small globule size.

Jha *et al.* (2022) conducted a study to examine mucoadhesive polymeric NPs of ZMT for intranasal administration to improve brain targeting and bioavailability during migraine attacks (116). With ZMT NPs, there is a significant increase in absolute bioavailability (193%) and better nasal-to-brain transport than with oral drug administration. It was found that adult male Swiss albino mice could tolerate reduced abdominal stretching and bright light in response to the treatment, indicating that the treatment is effective in reducing migraine symptoms. Intranasal delivery of NPs of ZMT appears to be a promising migraine treatment approach.

A 2020 study examined the Wistar albino rats given nasal sprays of chitosan NPs containing ZMT for pharmacokinetic studies (117). There was a significant increase in drug levels in plasma and brain tissue in the test formulation compared to the group receiving water for injection or standard drug solutions. Specifically, the test formulation shows a significant increase in the plasma concentrations (41.37 ± 2.31 ng/ml) compared to standard groups at 10 min post-administration (P<0.05). However, there was a significant increase in levels of drug absorption in brain tissue (15 ± 0.08 ng/g) compared to standard groups at 60 min post-administration (P<0.05). The findings indicate that nasal spray containing chitosan NPs loaded with ZMT may be effective at treating migraine headaches rapidly.

Researchers in 2022 performed a study to investigate SLNs to enhance ZMT delivery across the BBB (118). It has been found that SLNs possess favorable characteristics, such as high drug entrapment (84.17 x 12.24%), small size (110-200 nm), and stability, providing significant drug release both in vitro (95.85 x 2.44%) and in vivo (82.06 x 2.94%) over 24 hr. In vivo studies in male Wistar rats demonstrated enhanced pharmacokinetic parameters AUC (37.05 ± 2.45 ng/ml), Cmax (42.08 ± 1.32 ng/ml), and Tmax (30 min), t1/2 (1.28 hr)). Pharmacokinetic parameters indicate the effectiveness of intranasal delivery of ZT-loaded SLNs to bypass the hepatic metabolism, which improves the bioavailability and permeation of the drug, compared to oral administration.

Girotra *et al.* (2016) showed a quality-based design approach; PLGA/poloxamer NPs of ZMT were developed for brain delivery (106). In the optimized NPs, the size ranged from 165.4–245.4 nm, the encapsulation efficiency was 48.96-94.97%, and the drug release ranged from 43.32 to 100%. An analysis of the drug loading confirmed that there were no interactions between the drugs. The drug loading was confirmed to be successful without interactions based on the characterization. In vivo studies demonstrated a 14.13-fold increase in brain uptake compared to free drug, leading to significantly enhanced anti-migraine potential in Swiss albino mice. The findings suggest that ZMT-loaded PLGA/poloxamer NPs could effectively treat migraine.

A study conducted in 2018 examined and characterized nanostructured polymeric carriers for the direct administration of ZMT to the nose as a nose-to-brain target

Table 1. Summary of the studies about curcumin nanoformulations used for migraine

Nano formulation	Methods	Study model / Administration	Results	Ref.
Nano-curcumin and n-3 fatty acids	Measurement of migraine attack frequency and serum levels of IL-1β; comparison between individual treatments and combination	Human	Significant reduction in migraine attack frequency and serum levels of IL-1β with combination vs individual treatments (P<0.001). After modifications, a significant reduction in IL-1β gene expression was observed between combination and individual groups (P<0.05)	(113)
Liposomal curcumin and naproxen	Evaluation of anti-oxidant and anti-nociceptive actions; comparison with naproxen alone or curcumin solution in rat migraine models	Rat / intraperitoneal and intravenous	Significant reduction in oxidative stress markers and pain with a combination of naproxen (2.8 mg/kg) and liposomal curcumin (2 mg/0.1 kg) vs naproxen alone (P<0.001)	(114)
Omega-3 fatty acids and nano-curcumin	Analysis of iNOS/COX-2 levels and clinical symptoms in 74 migraine patients	Human	Significant reduction in iNOS/COX-2 levels and clinical symptoms with omega-3 and nano-curcumin vs control (P<0.05). It is promising for migraine prevention	(115)

for migraine treatment (119). Compared to intravenous and intranasal ZMT solutions, radiolabeled nanocarriers demonstrated improved characteristics and better brain uptake when administered via intranasal routes. The bimodal SPECT-CT scintigram results indicated that intranasal ZMT-loaded nanocarriers showed significant brain accumulation, suggesting their potential as migraine treatment systems.

Mohamed *et al*., 2019 performed a study investigating a liposomal formulation of ZMT for enhanced transdermal delivery, addressing systemic conditions like migraine and topical infections like mycotic (120). In addition to demonstrating small vesicle sizes (133.1 nm) and high entrapment efficiency (88.7%), the optimized formulation (F11) showed improved drug release. The F11-loaded emulsion gel significantly improved pharmacokinetic parameters and drug permeation over plain ZMT-loaded emulgel, suggesting it could treat various diseases.

A 2010 study examined micellar nanocarriers developed for nasal delivery of ZMT, and the transport pathway of the drug was investigated (121). A micellar nanocarrier was designed to deliver ZMT through the nasal passages, and its transport pathway was explored. A toxicity study in rats demonstrated no risks associated with nasal administration. Research on biodistribution demonstrated superior brain targeting over intravenous and nasal administration. A brain localization and autoradiography study has suggested that the drug labeled for consumption travels from the nose to the brain. The developed nanocarrier appears to be a promising vehicle for targeting ZMT in the brain.

Researchers in 2020 conducted a study to investigate a polymeric form of ZMT/chitosan nanostructured liposomes (ZT/CT NLCs) that are coated with Tween 80 to address the challenges associated with the use of ZMT (122). This formulation displayed high performance in terms of entrapment efficiency (78.14%), yield (60.19%), stability (0.28 mV), and negative zeta potential (-25.5 mV), resulting in good entrapment efficiency and yield. An application of NLCs to hard gelatin capsules in situ gelled for 30 hr and displayed pharmacological effectiveness for eight hours in mice, suggesting potential for improving other class III drugs' efficacy.

A 2022 study intended to increase the bioavailability of ZMT. This medication falls into class III of the BCS, as NLCs are used as a transdermal delivery system (123). Based on a factorial design, NLC9 was optimized to be the most favorable particle size, to exhibit the highest entrapment efficiency, and to release the most drug. By incorporating NLC9 into a gel, application stability and portability were enhanced. According to pharmacokinetic studies conducted in rabbits, ZMT has a 1.76-fold greater bioavailability than oral ZMT. A histopathological safety confirmation was obtained, suggesting that NLCs could benefit transdermal ZMT delivery and improve drug bioavailability.

A study (2021) showed the efficacy of ZMT while minimizing adverse effects by developing self-nano-emulsifying drug delivery systems for ZMT incorporating lavender oil (ZMT-SNEDDS) (124). As a result of the complete factorial design, the size of globules and zeta potential were optimized. ATR-FTIR monitoring of the optimized formulation (F5) confirmed superior dissolution and permeation, demonstrating safety in acute toxicity testing. Efficacy studies conducted on migraine rats have shown that F5 can significantly improve psychological state and pain relief while normalizing brain activity.

In 2016, a study examined ZMT-loaded nanoliposomes added to a thermos-reversible gel and mucoadhesive polymers added to facilitate nose-to-brain drug delivery via mucoadhesive polymers (125). Ethosomes with excellent characteristics were obtained, including formulation E6, which has an entrapment efficiency (66%) and optimal size (171.67 nm). A thermos-reversible gel based on poloxamer 407 showed sufficient phase transition temperatures. According to the histopathological analysis of the optimal formulations G3 and G6, these formulations demonstrated promising gel characteristics, *in vitro* release, *ex vivo* permeation, and non-toxic effects. Table 2 provides a summary of each study included in the review.

Sumatriptan

Hansraj *et al.* performed a study investigating sumatriptan succinate-containing SLNs developed for targeting the brain using chitosan SLNs (126). A complete factorial design was utilized to optimize the formulations so that all particle sizes and zeta potentials are minimized, entrapment efficiency is maximized, and the brain-to-plasma ratio is maximized. In rats, optimized SLNs increased the brain/blood drug ratio by 4.54-fold, indicating successful brain targeting. Various analytical techniques were used to characterize the formulation and confirm its efficacy and integrity. Ultimately, the study suggests that delivering sumatriptan succinate orally is an effective method of managing migraine.

Patravale *et al*., 2019 studied the advent of nanoformulations, which have attracted tremendous attention in recent decades due to their application in improving drug bioavailability (127). Microgels have several advantages, such as thermodynamic stability, ease of formulating, and enhanced penetration of biological barriers. These advantages make micellar nanosystems extremely useful in oral, transdermal, and parenteral administration. Additionally, they are being explored as noninvasive means of delivery, such as nose-to-brain. The purpose of this chapter is to describe a protocol for preparing sumatriptan-loaded micelles to treat migraine headaches. Micelles contain hydrophobic regions of diblock polymer that hold the drug and hydrophilic regions that provide conformational stability in aqueous environments.

Masjedi *et al.* performed a study to investigate a solution to the limitations of oral administration for migraine; sumatriptan-loaded NLCs were developed to deliver the drug nose-to-brain (128). Based on optimization, the NLCs had a mean diameter of 101 nanometers and a drug entrapment efficiency of 91.00%. Following intranasal administration, in vivo pharmacokinetic evaluations in rats showed significant Drug Targeting Efficiencies (DTEs) and Direct Transport Percentage (DTPs), indicating that NLC formulations have potential for brain delivery.

Researchers studied (2022) Nanoliposomes (NLs) coated with chitosan (CCLs), which were developed to enhance the bioavailability of the sumatriptan succinate (SS) in humans (129). The formulations were optimized by investigating their physicochemical properties and the associated pharmacokinetic parameters. Compared to SS and SS-NL, CCLs showed faster absorption and a shorter tmax than SS and SS-NL. The chitosan-coated NLs enhanced the absorption of SS, suggesting that drugs are delivered to the systemic circulation more effectively. According to the animal model, liposomal and chitosan formulations demonstrated better kinetic behavior than soluble forms.

Table 2. Summary of the studies about Zolmitriptan nanoformulations used for migraine

Nano formulation	Methods	Study model / Administration	Results	Ref.
Mucoadhesive nanoemulsions	Evaluation of ZMT mucoadhesive nanoemulsion viability, drug content, morphology, zeta potential, permeation, and pharmacokinetics in mice	Mice / intravenous and nasal	In mice, enhanced brain AUC and reduced Tmax were observed with mucoadhesive nanoemulsion, indicating improved brain delivery and rapid action compared to intravenous and nasal solutions	(112)
Mucoadhesive polymeric NPs	Assessment of ZMT NPs for intranasal administration in mice; evaluation of bioavailability, migraine symptom reduction	Mice / intranasal	Compared to oral administration, ZMT NPs significantly increased absolute bioavailability (193%) and improved nasal-to-brain transport. Reduced migraine symptoms were observed in mice, suggesting the efficacy of intranasal delivery for migraine treatment	(116)
Chitosan NPs	Pharmacokinetic study in Wistar albino rats receiving nasal sprays of chitosan NPs containing ZMT	Wistar albino rats / Nasal spray	Significant increase in plasma and brain tissue drug levels with chitosan NP nasal spray, indicating rapid absorption and potential efficacy in treating migraine	(117)
Solid Lipid Nanoparticles (SLNs)	Investigation of SLNs for ZMT delivery across the blood-brain barrier (BBB) in male Wistar rats	Male Wistar rats / intranasal	SLNs exhibited favorable characteristics and enhanced pharmacokinetic parameters, indicating improved bioavailability and permeation of ZMT. Promising intranasal delivery approach for bypassing hepatic metabolism and enhancing drug efficacy for migraine treatment	(118)
PLGA/poloxamer NPs	Development and characterization of ZMT-loaded NPs; evaluation of brain uptake in Swiss albino mice	Swiss albino mice / Intranasal	Optimized NPs showed increased brain uptake and enhanced anti-migraine potential compared to free drugs, indicating the potential efficacy of ZMT-loaded NPs in treating migraine	(106)
Polymeric carriers	Characterization and *in vivo* brain uptake evaluation of ZMT-loaded nanocarriers in rat migraine models	Rat / Intranasally	Improved brain uptake was observed with ZMT-loaded nanocarriers administered intranasally, suggesting their potential as migraine treatment systems	(119)
Liposomes	Development and characterization of ZMT/chitosan nanostructured liposomes; evaluation of pharmacological effectiveness	*Ex vivo*	ZMT/CT NLCs displayed good performance with high entrapment efficiency and stability, suggesting potential for improving drug efficacy in migraine treatment	(122)
Liposomes	Formulation and characterization of ZMT-loaded nanoliposomes; evaluation of mucoadhesive gel properties	*Ex vivo*	Nanoliposomes integrated into mucoadhesive gel exhibited promising characteristics, including good release, permeation, and non-toxic effects. This suggests the potential for effective nose-to-brain delivery of ZMT for migraine treatment	(125)

Yadav *et al.* investigated Sumatriptan succinate SLNPs, which were developed as nasal delivery vehicles for the drug (130). A central composite design was used using solvent injection to optimize formulation to minimize particle size, optimize zeta potential, and ensure maximum entrapment. Optimized batch parameters included 133.4 nm particle size, -17.7 mV zeta potential, and 75.5% entrapment efficiency. In the laboratory, the particle morphology was spherical, and the release of the drug was sustained for 12 hr. Diffusion studies *in vivo* showed rapid permeation across the nasal mucosa, indicating a brain target. It was confirmed histopathologically that the nasal mucosa was intact after treatment. As a result, SLNPs may be a promising delivery method for sumatriptan succinate nasally.

Girotra *et al.*, in 2016, performed a study to optimize the performance of PBCA NPs for the delivery of sumatriptan succinate to the brain and compare them to SS-loaded BSA-ApoE NPs (131). A central composite design optimizes the size and release of the PBCA NPs. There was a higher brain uptake of SS-AA-NP in rats than in FPopt in *in vivo* studies. Mice behavioral tests confirmed SS-AA-NP's superior antimigraine potential. There is a potential for better brain targeting of SS with BSA-ApoE NPs in migraine treatment.

In 2018, a study was conducted to investigate the effects of liposomal curcumin at a dose of 2 mg/100 g body weight in combination with sumatriptan in an experimental migraine model induced by nitroglycerin in rats (132). Researchers demonstrated significant reductions in plasma total oxidative stress levels, malondialdehyde levels, and nitric oxide levels following the treatment. Moreover, liposomal curcumin was found to have superior antioxidative properties compared with curcumin solution, which suggests that liposomal curcumin could be an optimal treatment method for migraine, warranting further research.

A 2020 study examined an intranasal formulation containing copaiba oil and biopolymers developed to enhance the delivery of sumatriptan in treating migraine (133). A stable Nano Emulsion (NE) that demonstrates favorable properties after over a year of use can prolong sumatriptan release by more than 24 hr. An in vivo test in zebrafish confirmed the safety of both the alginate-based NE and its potential efficacy, suggesting that it may be able to treat migraine pain.

In 2017, researchers investigated the hydrothermal synthesis of magnetic porous carriers based on tin oxide nanocrystals (134). This material had a high magnetization and a uniform particle size of 65 nm. Studies showed that the drug release of Sumatriptan, an anti-migraine drug, can be efficient and controlled remotely. The optimal drug efficiency (70%) was achieved with specific parameters. *In vitro* studies and stability testing confirmed that the carrier is

appropriate for in vivo applications. Table 3 shows a summary of sumatriptan nanoformulations used for migraine.

Others

Harjot *et al.* performed a study to investigate an aerosol drug delivery system for flunarizine dihydrochloride that would improve solubility and therapeutic effect (109). A compatibility study confirmed the formulation's suitability (110). Moreover, Nystatin-loaded chitosan NPs administered intraperitoneally in rats also demonstrated enhanced brain targeting and reduced migraine-associated behaviors like hyperalgesia, photophobia, and phonophobia compared to free drug (135). This represents a novel approach using the antifungal drug nystatin for migraine treatment.

Dali *et al.* conducted a study to examine ergotamine and caffeine hybrid NPs that were PEGylated lipid-polymer hybrids, focusing on controlled release, entrapment efficiency, and permeability (107). Nanoparticles produced using a single-step nanoprecipitation method had favorable characteristics, including good stability, small size (239.46 2.31 nm), controlled release profile, and high entrapment efficiency (86.88 1.67%). *In vitro* and *ex vivo* studies indicate sustained release over 48 hr following intranasal administration and significant brain uptake post-intranasal administration, with histopathologic and toxicological studies confirming safety and anti-hyperalgesia. There was potential for the formulation to be used to treat migraine.

Furthermore, sumatriptan succinate-loaded chitosan NPs developed using the Taguchi optimization method showed favorable characteristics for intranasal delivery, including a mean size of 306.8 nm, positive zeta potential of +28.79 mV, and 75.4% drug entrapment efficiency (136). The *in vitro* release of sumatriptan from these NPs through goat nasal mucosa was 76.7% over 28 hr, indicating their potential for improved bioavailability and therapeutic effect compared to the free drug.

Abou Youssef *et al.* performed a study to investigate a safe and efficient system for delivering the water-soluble anti-migraine medicine Almotriptan Malate (ALM) intranasally (137). As a result of a double-emulsion-solvent evaporation process, SLNs were prepared and optimized for entrapment efficiency, polydispersity index, and particle

Table 3. Summary of the studies about Sumatriptan nanoformulations used for migraine

Nano formulation	Methods	Study model / Administration	Results	Ref.
Micelles	Description of protocol for preparing sumatriptan-loaded micelles for migraine treatment; characterization of micelles	Oral, transdermal, and parenteral administration	Micelles provide potential noninvasive delivery for migraine treatment, offering advantages of oral, transdermal, and parenteral administration. Hydrophobic regions of diblock polymer hold the drug, while hydrophilic regions provide conformational stability in aqueous environments, making micelles useful in various administration routes	(127)
NLCs	Development of NLCs for nose-to-brain delivery of sumatriptan; optimization of formulation parameters; *in vivo* pharmacokinetic evaluations in rats	Rat /Intranasal	Optimized NLCs demonstrated significant Drug-Targeting Efficiencies (DTEs) and Direct Transport Percentages (DTPs) in rats, indicating the potential for brain delivery of sumatriptan	(128)
Chitosan-coated nanoliposomes	Formulation optimization and pharmacokinetic evaluation of chitosan-coated nanoliposomes for enhanced bioavailability of sumatriptan succinate	White New Zealand male rabbits / Internasal	Chitosan-coated NLs enhanced sumatriptan absorption, leading to faster absorption and improved systemic delivery compared to soluble forms. Animal studies showed better kinetic behavior of liposomal and chitosan formulations, indicating their potential for improving sumatriptan bioavailability and efficacy in migraine treatment	(129)
PBCA NPs and SS-loaded BSA-ApoE NPs	Optimization of PBCA NPs and SS-loaded BSA-ApoE NPs for brain delivery of sumatriptan succinate; comparison of brain uptake and antimigraine potential in rats	Rats /Internasal	SS-loaded BSA-ApoE NPs showed higher brain uptake and superior antimigraine potential than PBCA NPs in rats, indicating the potential for improved brain targeting of sumatriptan succinate in migraine treatment	(131)
Liposomal	Investigation of combination treatment with liposomal curcumin and sumatriptan in experimental migraine model induced by nitroglycerin in rats	Rats /Intravenous	Liposomal curcumin combined with sumatriptan significantly reduced oxidative stress levels, suggesting potential as an optimal treatment method for migraine. The superior antioxidative properties of liposomal curcumin compared with curcumin solution indicate its promise in migraine therapy, warranting further research	(132)
Nanoemulsion	Development of stable Nano Emulsion (NE) containing copaiba oil and biopolymers; evaluation of NE properties and *in vivo* efficacy in zebrafish	Zebrafish / Intranasal	Stable NE prolonged sumatriptan release for over 24 hr and demonstrated safety and potential efficacy in zebrafish, suggesting its potential in treating migraine pain	(133)
Magnetic porous carriers	Synthesis of magnetic porous carriers based on tin oxide nanocrystals for efficient and controlled drug release of sumatriptan; characterization and stability testing	*Ex vivo*	Optimal drug efficiency (70%) was achieved with magnetic porous carriers based on tin oxide nanocrystals, demonstrating efficient and controlled drug release. *In vitro* studies and stability testing confirmed the suitability of carriers for *in vivo* applications, suggesting their potential for enhancing sumatriptan delivery in migraine treatment	(134)

size. A mucoadhesive in situ gel contained Na-CMC and Poloxamer 407, which included the optimized SLNs dispersed within the gel. ALM was rapidly delivered into the brain through the formulated system, with promising results in both in vitro and in vivo studies and favorable toxicological risk profiles. As a result of these findings, it is possible to conduct future clinical trials using the delivery system developed in humans with positive results.

A 2020 study investigated whether chitosan-coated NLCs can effectively deliver Almotriptan maleate (ALM) through nasal mucosa (138). During formulation optimization, the final formula (F1) showed favorable properties regarding zeta potential (34.1 mV), particle size (255 nm), entrapment efficiency (80%), and PDI (0.27). Studies on the compounds' in vivo and in vitro release and their mucoadhesive properties resulted in increased brain uptake, with histopathological evaluation confirming their safety.

Hadel *et al.* performed a study to investigate the occurrence of migraine, which is often accompanied by psychiatric disorders such as anxiety and depression (139). Eletriptan hydrobromide (EH) is not absorbed enough orally to reach the brain effectively. A nasal assemblesymptoms rapidly and effectively. The formulations were optimized using thin-film hydrolysis and factorial design to maximize zeta potential, entrapment efficiency, and particle size. According to in vitro studies, permeability was enhanced with a favorable residence time. Three months were required for EH emulsions to be stable. EH was effectively delivered through the nose to the CNS without causing any damage to the nasal mucosa in vivo, confirming their efficacy and safety.

In 2017, a study investigated rizatriptan benzoate's anti-migraine potential by using SLNs to target brain regions (140). Critical formulation variables that affected RB-SLN fabrication were identified in the Plackett-Burman formulation. SLNs with a Box-Behnken design have been found to have a size of 220.4 2.3 nm, an entrapment efficiency of 71.8 1.9%, as well as a cumulative release rate of 45.9 2.7% after 8 hr. By determining the structure of the SLN using TEM images, XRD, thermal analysis, and FTIR spectroscopy, the SLN structure has been confirmed. Following oral administration for 2 hr, in vivo studies have demonstrated an 18.43-fold increase in brain uptake compared to free drugs. It was shown in pharmacodynamic studies of Swiss albino mice that RB-SLNs possess enhanced anti-migraine efficacy, suggesting their potential as migraine remedies.

A 2023 study investigated dissolving microneedles containing caffeine and ergotamine, which were developed as a synergistic migraine treatment (141). Microneedles were created by incorporating drug-loaded Poly Lactic-co-Glycolic Acid (PLGA) nanospheres into a polymer matrix and integrating them into the polymer matrix. As a result of their narrow size distributions and good stability, the nanospheres were highly entrappable and controlled when released. Microneedles produced sustained release both *ex vivo* and *in vitro*, with antihyperalgesic activity and nontoxicity confirmed by serotonin and histopathology tests. A new 3D applicator effectively delivers intranasal migraine medications into the nasal cavity, making it a promising approach for treating the condition. Table 4 shows a summary of the other nanoformulations used for migraine.

Challenges and future directions in nanoformulation for migraine treatment

Several challenges must be overcome to enhance migraine treatment through nanoformulation. Furthermore, research efforts are underway to identify innovative strategies for overcoming these challenges and advancing migraine therapy with nanoformulation (142).

Challenges

Migraine therapy faces several challenges, one of which is ensuring that the drugs delivered to the CNS, which is the primary site of migraine pathology, are effective (143). The BBB limits therapeutic delivery to the brain parenchyma, which limits migraine medications' effectiveness. Developing nanoformulations that can penetrate the BBB and deliver drugs to the desired target sites within the CNS is a challenging endeavor that requires innovative strategies to maximize penetration within the BBB while minimizing adverse effects off-target. A significant aspect of clinical translation is ensuring the safety and biocompatibility of nanoformulations (144). However, despite their advantages in drug delivery and targeting, there needs to be more concern regarding the long-term effects of NPs' potential toxicity and immunogenicity on biological systems. To minimize the danger of adverse effects and guarantee patient safety, researchers must carefully evaluate the biocompatibility of nanocarriers and their degradation products. Increasing the cost-effectiveness, reproducibility, and quality control of nanoformulations for clinical use are significant challenges. Standardized protocols are crucial in transitioning from laboratory to large-scale production to ensure consistently high product quality and performance. Furthermore, a nanoformulation formulation method and manufacturing technique can impact its properties and performance, which require optimization and validation throughout development (47). Achieving regulatory approval for nanoformulations in light of their novelty and complexity presents a unique challenge. For regulators to evaluate nanoformulations for quality, safety, and efficacy and their comparability to conventional therapies, comprehensive preclinical and clinical data is required (145). Successful regulatory approval and clinical translation require demonstrating bioequivalence between nanoformulations and existing therapies, addressing potential immunogenicity concerns, and addressing biodistribution issues. As nanoformulations are developed and manufactured at high cost, widespread adoption and accessibility may be hindered, especially in places with limited resources. Regulatory compliance, nanomaterials, and specialized equipment can increase production costs, limiting patient access to innovative therapies (146). Consequently, maximizing manufacturing processes, reducing production costs, and streamlining regulatory procedures are crucial to ensuring migraine nanoformulations are affordable and accessible.

Future directions

In the future, researchers should investigate novel strategies that will improve drug delivery to the central nervous system and enhance the penetration of the BBB. Multifunctional nanocarriers capable of actively reaching and crossing the BBB may be designed, as well as non-invasive treatment methods such as intranasal administration or focused ultrasounds that can open the BBB (13). Furthermore, advances in nanotechnology, including the development of stimuli-responsive and self-assembling NPs, could provide an innovative way to enhance BBB penetration within a patient's brain and improve drug distribution within the

Table 4. Other nanoformulations used for migraine

Nano formulation used	Methods	Study model / Administration	Results	Ref.
Aerosol drug delivery system for flunarizine dihydrochloride	Investigation of compatibility study and formulation suitability	*Ex vivo*	The Aerosol drug delivery system for flunarizine dihydrochloride is confirmed to be suitable with compatibility study, suggesting potential for improving solubility and therapeutic effect	(109)
PEGylated lipid-polymer hybrid nanoparticles	Production of ergotamine and caffeine hybrid NPs; characterization and evaluation of controlled release, entrapment efficiency, and permeability	Mice / Internasal	NPs exhibited favorable characteristics, including good stability, small size, controlled release profile, high entrapment efficiency, sustained release over 48 hr post-intranasal administration, and significant brain uptake. They confirmed the safety and anti-hyperalgesic effects, indicating the potential for treating migraine	(107)
Solid lipid nanoparticles (SLNs) + mucoadhesive *in situ* gel	Preparation and optimization of SLNs loaded with Almotriptan Malate (ALM); development of mucoadhesive *in situ* gel containing the optimized SLNs; evaluation of delivery system efficacy and safety	Rat/Internasal	SLN-loaded *in situ* gel rapidly delivered ALM into the brain, with promising results in both *in vitro* and *in vivo* studies and favorable toxicological risk profiles, indicating potential for future clinical trials and positive outcomes in human migraine treatment	(137)
Chitosan-coated nanostructured lipid carriers (NLCs)	Formulation optimization and evaluation of chitosan-coated NLCs for Almotriptan maleate (ALM) delivery through nasal mucosa	Albino rabbits/Internasal	Formulated chitosan-coated NLCs showed favorable properties and increased brain uptake, with histopathological evaluation confirming safety, suggesting potential for effective delivery of ALM through nasal mucosa for migraine treatment	(138)
Solid lipid nanoparticles (SLNs) for rizatriptan benzoate	Identification of critical formulation variables and optimization of SLNs for rizatriptan benzoate delivery; characterization and evaluation of brain uptake and anti-migraine efficacy	Swiss albino mice/Internasal	Optimized SLNs demonstrated favorable characteristics and enhanced brain uptake, with significant anti-migraine efficacy demonstrated in pharmacodynamic studies, indicating their potential as migraine remedies	(140)
Dissolving microneedles containing caffeine and ergotamine	Development of dissolving microneedles containing caffeine and ergotamine for migraine treatment; characterization and evaluation of sustained release and safety	*In vitro* and *ex vivo*	Microneedles produced sustained release, antihyperalgesic activity, and confirmed safety. A new 3D applicator effectively delivered intranasal migraine medications into the nasal cavity, suggesting a promising approach for treating migraine	(141)

body. Advancements in nanotechnology make it possible to target therapeutics precisely to the cells or molecular targets involved in migraine pathogenesis (147). In the future, nanoformulations may include surface modifications or targeting ligands to improve their affinity for diseased cells or receptors, improving therapeutic efficacy while minimizing off-target effects. Using receptor-mediated endocytosis and molecular recognition, researchers can develop nanocarriers to selectively deliver drugs to migraine-specific targets, such as inflammation mediators, trigeminal neurons, and glial cells (118). Researchers are pursuing the development of personalized nanoformulations designed based on the characteristics of patients and their responses to treatment. The system integrates patient-specific data, such as imaging findings, biomarker expression patterns, and genetic profiles, to design nanoformulations tailored to patients' needs and disease characteristics (46). With the use of custom medicine approaches, migraine patients may receive more precise dosing regimens, suffer fewer adverse effects, and have better treatment outcomes, ultimately leading to a paradigm shift towards migraine precision therapy (148). When multiple therapeutic agents are combined in a single nanoformulation, beneficial synergistic effects can be achieved, and the therapeutic outcome can be improved. A combination of analgesics, anti-inflammatory agents, neuroprotectant agents, and neuromodulators may be incorporated into future migraine nanoformulations. A combination of drugs with complementary mechanisms enhances pain relief, reduces inflammation, and prevents migraine attacks more effectively than monotherapies (13). In addition, taking advantage of the co-delivery of therapeutic agents within nanoformulations and imaging probes may help monitor disease progression and treatment response in real-time, facilitating customized therapeutic interventions and improving patient care (109). Furthermore, nanotechnology provides opportunities to develop advanced diagnostic tools to diagnose, monitor, and prognosis migraine. Biomarkers, imaging agents, and biosensors based on NPs can give insight into the pathophysiology of disease, identify disease biomarkers, and provide non-invasive treatment response monitoring (146). A nanotechnology-enabled diagnostic that integrates specificity, sensitivity, and multiplexing capabilities may improve therapeutic decision-making, patient stratification, and migraine management.

Conclusion

Nanoformulation emerges as a promising frontier in addressing the complex and debilitating nature of migraine, offering a potential solution to overcome the limitations of conventional treatments. By encapsulating therapeutic agents within nanocarriers and modulating their properties, nanoformulation optimizes drug delivery, enhances bioavailability, and minimizes adverse effects, providing superior efficacy compared to traditional medications, lifestyle changes, and behavioral therapies.

While conventional treatments may offer symptomatic relief, nanoformulation stands out for its ability to target specific mechanisms underlying migraine attacks, such as neuroinflammation or neurotransmitter imbalances, and enable personalized medicine approaches tailored to individual patient needs. Despite challenges related to safety, biocompatibility, scalability, and regulatory approval, ongoing research efforts continue to advance the field of nanoformulation for migraine therapy. Future directions include enhancing blood-brain barrier penetration, developing nanotechnology-enabled diagnostics, and incorporating personalized medicine approaches to optimize patient outcomes. In conclusion, nanoformulation holds the potential to revolutionize migraine treatment, offering patients personalized and precise therapies that improve their quality of life and overall well-being.

Authors' Contributions

GN M collected data, discussed the results, and prepared a draft manuscript, H M supervised, directed, and managed the study, S Z, K F, and M S checked and approved the final version of the manuscript for publication in the present journal.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

All applicable international, national, and/or institutional guidelines for writing review papers were followed.

References

1. Gupta J, Gaurkar SS. Migraine: An underestimated neurological condition affecting billions. Cureus 2022;14:e28347.
2. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A, *et al.* Migraine: Epidemiology and systems of care. The Lancet 2021;397:1485-1495.
3. Khan J, Al Asoom LI, Al Sunni A, Rafique N, Latif R, Al Saif S, *et al.* Genetics, pathophysiology, diagnosis, treatment, management, and prevention of migraine. Biomed Pharmacother 2021;139:111557.
4. Russo AF, Hay DL. CGRP physiology, pharmacology, and therapeutic targets: Migraine and beyond Physiolog Rev 2023;103:1565-1644.
5. Hendrix C. Migraine-Prophylactic and Acute Migraine Treatments. Evidence-Based Use of Supplements 2021;4: 1-9.
6. Nicholson RA, Buse DC, Andrasik F, Lipton RB. Nonpharmacologic treatments for migraine and tension-type headache: how to choose and when to use. Curr Treat Option Neurol 2011;13:28-40.
7. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. Springerplus 2016;5:637-650.
8. Society AH. The American Headache Society position statement on integrating new migraine treatments into clinical practice. Headache: J Head Face Pain 2019;59:1-18.
9. Ailani J, Burch RC, Robbins MS, Society BoDotAH. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: J Head Face Pain 2021;61:1021-1039.
10. Singh R, Brumlik C, Vaidya M, Choudhury A. A patent review on nanotechnology-based nose-to-brain drug delivery. Recent Pat Nanotechnol 2020;14:174-192.
11. Vlieghe P, Khrestchatisky M. Medicinal chemistry based approaches and nanotechnology-based systems to improve CNS drug targeting and delivery. Med Res Rev 2013;33:457-516.
12. Sadr S, Lotfalizadeh N, Abbasi AM, Soleymani N, Hajjafari A, Roohbaksh Amooli Moghadam E, *et al.* Challenges and prospective of enhancing hydatid cyst chemotherapy by nanotechnology and the future of nanobiosensors for diagnosis. Trop Med Infect Dis 2023;8:494-515.
13. Bahadur S, Jha MK. Emerging nanoformulations for drug targeting to brain through intranasal delivery: A comprehensive review. J Drug Deliv Sci Technol 2022:103932
14. Pandey A, Nikam A, Basavraj S, Mutalik S, Gopalan D, Kulkarni S, *et al.* Nose-to-brain drug delivery: Regulatory aspects, clinical trials, patents, and future perspectives. Direct nose-to-brain drug delivery: Elsevier; 2021. p. 495-522.
15. Kumar S, Singh P, Sharma S, Pottoo FH, Ali J, Baboota S. Envisioning the future of nanomedicines in management and treatment of neurological disorders. Comb Chem High Throughput Screen 2021;24:1544-1556.
16. Virmani R, Virmani T, Pathak K. Nanovesicles for delivery of central nervous system drugs. Applications of Nanovesicular Drug Delivery: Elsevier; 2022. 315-339.
17. Akhtar A, Andleeb A, Waris TS, Bazzar M, Moradi A-R, Awan NR, *et al.* Neurodegenerative diseases and effective drug delivery: A review of challenges and novel therapeutics. J Control Release 2021;330:1152-1167.
18. Sadr S, Poorjafari Jafroodi P, Haratizadeh MJ, Ghasemi Z, Borji H, Hajjafari A. Current status of nano-vaccinology in veterinary medicine science. Vet Med Sci 2023;9:2294-2308.
19. Wu D-D, Ahmed SY, Erasto NE, Zhang Y-X, Khattak S, Hussain KN, *et al.* Nanotechnology prospects in brain therapeutics concerning gene-targeting and nose-to-brain administration. Iscience 2023; 18; 26: 107321.
20. Tanna V, Sawarkar SP, Ravikumar P. Exploring nose to brain nano delivery for effective management of migraine. Curr Drug Deliv 2023;20:144-157.
21. Lade S, Shah N, Burle S. Nanostructured lipid carriers: A vital drug carrier for migraine treatment. Res J Pharm Technol 2022;15:3309-3016.
22. Sachan N, Bahadur S, Sharma PK. Recent advances and novel approaches for nose to brain drug delivery for treatment of migraine. Drug Deliv Let 2019;9:182-198.
23. Minen M, Shome A, Halpern A, Tishler L, Brennan K, Loder E, *et al.* A migraine management training program for primary care providers: An overview of a survey and pilot study findings, lessons learned, and considerations for further research. Headache: J Head Face Pain 2016;56:725-740.
24. Kesserwani H, Kesserwani HN. Migraine triggers: An overview of the pharmacology, biochemistry, atmospherics, and their effects on neural networks. Cureus 2021;13:e14243.
25. Rapoport AM, Lin T. Device profile of the Nerivio™ for acute migraine treatment: Overview of its efficacy and safety. Exp Rev Med Dev 2019;16:1017-1023.
26. F Gasparini C, G Sutherland H, R Griffiths L. Studies on the pathophysiology and genetic basis of migraine. Curr Genom 2013;14:300-315.
27. Curone M, Tullo V, Didier HA, Bussone G. Overview on

effectiveness of erenumab, fremanezumab, and galcanezumab in reducing medication overuse headache in chronic migraine patients. Neurolog Sci 2022;43:5759-5761.
28. Sudershan A, Mahajan K, Singh K, Dhar MK, Kumar P. The complexities of migraine: a debate among migraine researchers: a review. Clin Neurol Neurosurg 2022;214:107136.
29. Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults-overview of Cochrane reviews. Cochrane Database Syst Rev 2014; 2014:CD009108.
30. Minen MT, De Dhaem OB, Van Diest AK, Powers S, Schwedt TJ, Lipton R, *et al*. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psych 2016;87:741-749.
31. Yeh P-K, An Y-C, Hung K-S, Yang F-C. Influences of genetic and environmental factors on chronic migraine: A narrative review. Curr Pain Headache Rep 2024; 28:169-180.
32. Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. New England J Med 2002;346:257-270.
33. Li Y-X, Xiao X-l, Zhong D-L, Luo L-J, Yang H, Zhou J, *et al*. Effectiveness and safety of acupuncture for migraine: An overview of systematic reviews. Pain Res Manag 2020; 2020:3825617.
34. Zhang X-t, Li X-y, Zhao C, Hu Y-y, Lin Y-y, Chen H-q, *et al*. An overview of systematic reviews of randomized controlled trials on acupuncture treating migraine. Pain Res Manag 2019; 2019:5930627.
35. Jan MM. Updated overview of pediatric headache and migraine. Saudi Med J 2007;28:1324-1329.
36. Puledda F, Silva EM, Suwanlaong K, Goadsby PJ. Migraine: From pathophysiology to treatment. J Neurol 2023; 270:3654-3666.
37. Green MW. Overview of migraine: Recognition, diagnosis, and pathophysiology. Headache Migraine Biol Manag, Elsevier; 2015. 41-9.
38. Peters GL. Migraine overview and summary of current and emerging treatment options. Am J Manag Care 2019;25:S23-S34.
39. Muthyala N, Qadrie Z, Suman A. Migraine & migraine management: A review. PharmaTutor 2018; 6:8-17.
40. Ravisankar P, Hundia A, Sindhura J, Rani BS, Sai P. Migraine-A comprehensive review. J Pharma Res 2015; 5:1-20
41. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM, *et al*. Ubrogepant for the treatment of migraine. New England J Med 2019; 381:2230-2241.
42. Olla D, Sawyer J, Sommer N, Moore JB. Migraine treatment. Clin Plastic Surg 2020;47:295-303.
43. Silberstein SD. Preventive migraine treatment. Continuum 2015;21: 973-989.
44. Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment? Headache: J Head Face Pain 2002;42:3-9.
45. Negro A, Martelletti P. Gepants for the treatment of migraine. Exp Opin Investigat Drugs 2019;28:555-567.
46. Tardiolo G, Bramanti P, Mazzon E. Migraine: experimental models and novel therapeutic approaches. Int J Mol Sci 2019;20:2932-2951.
47. Alexander A, Agrawal M, Chougule MB, Saraf S, Saraf S. Nose-to-brain drug delivery: An alternative approach for effective brain drug targeting. Nanopharmaceuticals: Elsevier; 2020. 175- 200.
48. Becker WJ. Acute migraine treatment. Continuum: Lifelong Learning in Neurology 2015;21:953-972.
49. Pardutz A, Schoenen J. NSAIDs in the acute treatment of migraine: A review of clinical and experimental data. Pharmaceuticals 2010;3:1966-1987.
50. Leroux E, Buchanan A, Lombard L, Loo LS, Bridge D, Rousseau B, *et al*. Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: A systematic literature review. Adv Ther 2020;37:4765-4796.
51. Yang C-P, Liang C-S, Chang C-M, Yang C-C, Shih P-H, Yau Y-C, *et al*. Comparison of new pharmacologic agents with triptans for treatment of migraine: a systematic review and meta-analysis. JAMA Network Open 2021;4:e2128544-e.
52. Orlova YY, Mehla S, Chua AL. Drug safety in episodic migraine management in adults part 1: Acute treatments. Curr Pain Headache Rep 2022;26:481-492.
53. Ramachanderan R, Schramm S, Schaefer B. Migraine drugs ChemTexts. 2023;9:1-66.
54. Konstantinos S, Vikelis M, Rapoport A. Acute care and treatment of migraine. J Neuro-Ophthalmol 2020;40:472-484.
55. Peck J, Urits I, Zeien J, Hoebee S, Mousa M, Alattar H, *et al*. A comprehensive review of over-the-counter treatment for chronic migraine headaches. Curr Pain Headache Rep 2020;24:1-9.
56. Chiang C-C, Schwedt TJ. Calcitonin gene-related peptide (CGRP)-targeted therapies as preventive and acute treatments for migraine—the monoclonal antibodies and gepants. Prog Brain Res 2020;255:143-170.
57. Maasumi K, Michael RL, Rapoport AM. CGRP and migraine: The role of blocking calcitonin gene-related peptide ligand and receptor in the management of migraine. Drugs 2018;78:913-928.
58. Tepper SJ. History and review of anti-calcitonin gene-related peptide (CGRP) therapies: From translational research to treatment. Headache: J Head Face Pain 2018;58:238-275.
59. Ray JC, Kapoor M, Stark RJ, Wang S-J, Bendtsen L, Matharu M, *et al*. Calcitonin gene related peptide in migraine: Current therapeutics, future implications and potential off-target effects. J Neurol Neurosurgery & Psychiatry 2021;92:1325-1334.
60. Edvinsson L. The CGRP pathway in migraine as a viable target for therapies. Headache: J Head Face Pain 2018;58:33-47.
61. Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: A new era in migraine therapy. Lancet 2019; 394:1765-1774.
62. Edvinsson L. Calcitonin gene-related peptide (CGRP) is a key molecule released in acute migraine attacks—Successful translation of basic science to clinical practice. J Int Med 2022;292:575-586.
63. Jackson JL, Kuriyama A, Kuwatsuka Y, Nickoloff S, Storch D, Jackson W, *et al*. Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis. PLoS One 2019;14:e0212785.
64. Danesh A, Gottschalk PCH. Beta-blockers for migraine prevention: A review article. Curr Treat Options Neurol 2019;21:1-13.
65. Lai K-L, Pan L-LH, Liao K-K, Chen W-T. Electrophysiological basis for antiepileptic drugs in migraine prevention. Progress Brain Res 2020;255:69-97.
66. Al-Karagholi MA-M, Gram C, Nielsen CAW, Ashina M. Targeting BK Ca channels in Migraine: Rationale and perspectives. CNS Drugs 2020;34:325-335.
67. Al-Karagholi MA-M, Ghanizada H, Nielsen CAW, Skandarioon C, Snellman J, Lopez-Lopez C, *et al*. Opening of BKCa channels causes migraine attacks: A new downstream target for the treatment of migraine. Pain 2021;162:2512-2520.
68. Kowalska M, Prendecki M, Piekut T, Kozubski W, Dorszewska J. Migraine: Calcium channels and glia. Int J Mol Sci 2021;22:2688-2703.
69. Lampl C, MaassenVanDenBrink A, Deligianni CI, Gil- Gouveia R, Jassal T, Sanchez-del-Rio M, *et al*. The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis. J Headache Pain 2023;24:1-14.
70. Becker WJ. Botulinum toxin in the treatment of headache. Toxins 2020;12:803-813.
71. Marcelo R, Freund B. The efficacy of botulinum toxin in pediatric chronic migraine: a literature review. J Child Neurol 2020;35:844-851.
72. Martinelli D, Arceri S, Tronconi L, Tassorelli C. Chronic migraine and Botulinum Toxin Type A: Where do paths cross? Toxicon 2020;178:69-76.
73. Sohita D. Zavegepant: First Approval, Drugs 2023; 83: 825– 831
74. Dong G, Kjærgaard NA, Shakibfar S, Sessa M. Ubrogepant and

rimegepant: Systematic review, meta-analysis, and meta-regression of clinical studies. Expert Opin Drug Saf 2023;22:59-70.
75. Claudio T, Francesco C, Maria AG. New Therapeutic Options for Migraine 2023; 29:1964-1966.
76. Hay DL, Walker CS, Harris PWR. Atogepant (Qulipta) for migraine prevention. Trends Pharmacol Sci 2022; 43:701-702.
77. Van Der Arend BWH, Van Veelen N, De Ruijter JET, Olsen MH, MaassenVanDenBrink A, Terwindt GM. Safety considerations in the treatment with anti-CGRP(R) monoclonal antibodies in patients with migraine. Front Neurol 2024;15:1387044.
78. Frank F, Ulmer H, Sidoroff V, Broessner G. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: A systematic review and meta-analysis. Cephalalgia 2021;4:1222-1239.
79. Tanaka M, Tuka B, Vécse L. Navigating the Neurobiology of Migraine: From Pathways to Potential Therapies. Cells 2024; 13:1098-1110.
80. Tundisi LL, Ataide JA, Costa JSR, de Freitas Coêlho D, Liszbinski RB, Lopes AM, *et al.* Nanotechnology as a tool to overcome macromolecules delivery issues. Colloids and Surfaces B: Biointerfaces 2023;222:113043.
81. Yaqoob SB, Adnan R, Rameez Khan RM, Rashid M. Gold, silver, and palladium nanoparticles: a chemical tool for biomedical applications. Front Chem 2020;8:376-390.
82. Alebooye LF, Hafezi GZ, Alibolandi M, Ebrahimian M, Hashemi M. Evaluation of the effect of crocetin on antitumor activity of doxorubicin encapsulated in PLGA nanoparticles. Nanomed J 2016; 3:23-34.
83. Saeed M, Sadr S, Gharib A, Lotfalizadeh N, Hajjafari A, Simab PA, *et al.* Phytosomes: A promising nanocarrier for enhanced delivery of herbal compounds in cancer therapy. J Lab Anim Res 2022;1:26-32.
84. Leon L, Chung EJ, Rinaldi C. A brief history of nanotechnology and introduction to nanoparticles for biomedical applications. Nanoparticles for biomedical applications: Elsevier; 2020. 1-4.
85. Sim S, Wong NK. Nanotechnology and its use in imaging and drug delivery. Biomed Rep 2021;14:1-9.
86. Sahu T, Ratre YK, Chauhan S, Bhaskar L, Nair MP, Verma HK. Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. J Drug Deliv Sci Technol 2021;63:102487.
87. Gottardo S, Mech A, Drbohlavová J, Małyska A, Bøwadt S, Sintes JR, *et al.* Towards safe and sustainable innovation in nanotechnology: State-of-play for smart nanomaterials. NanoImpact 2021;21:100297.
88. Safavinia A, Dehestani S, Salmasi Z, Kalalinia F, Etemad L, Hashemi M. Recent advances in nanocarriers containing Bromelain: *In vitro* and *in vivo* studies. Nanomed J 2023;10: 163-170.
89. Shahgordi S, Oroojalian F, Hashemi E, Hashemi M. Recent advances in development of nano-carriers for immunogene therapy in various complex disorders. Iran J Basic Med Sci 2022;25:134-147.
90. Pramanik PKD, Solanki A, Debnath A, Nayyar A, El- Sappagh S, Kwak K-S. Advancing modern healthcare with nanotechnology, nanobiosensors, and internet of nano things: Taxonomies, applications, architecture, and challenges. IEEE Access 2020;8:65230-65266.
91. Negahdari R, Bohlouli S, Sharifi S, Maleki Dizaj S, Rahbar Saadat Y, Khezri K, *et al.* Therapeutic benefits of rutin and its nanoformulations. Phytother Res 2021;35:1719-1738.
92. Ghasemiyeh P, Mohammadi-Samani S. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: Applications, advantages and disadvantages. Res Pharmaceut Sci 2018;13:288-303.
93. Jamkhande PG, Ghule NW, Bamer AH, Kalaskar MG. Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. J Drug Deliv Sci Technol 2019;53:101174.
94. Natarajan JV, Nugraha C, Ng XW, Venkatraman S. Sustained-release from nanocarriers: A review. J Control Release 2014;193:122-138.
95. Herdiana Y, Wathoni N, Shamsuddin S, Muchtaridi M. Drug release study of the chitosan-based nanoparticles. Heliyon 2022; 8: e08674.
96. Jayant RD, Atluri VS, Agudelo M, Sagar V, Kaushik A, Nair M. Sustained-release nanoART formulation for the treatment of neuroAIDS. Int J Nanomed 2015;1077-1093.
97. Khan AR, Yang X, Fu M, Zhai G. Recent progress of drug nanoformulations targeting to brain. J Control Release 2018;291:37-64.
98. Agrahari V, Burnouf P-A, Burnouf T, Agrahari V. Nanoformulation properties, characterization, and behavior in complex biological matrices: Challenges and opportunities for brain-targeted drug delivery applications and enhanced translational potential. Adv Drug Deliv Rev 2019;148:146-180.
99. Kumari S, Goyal A, Sönmez Gürer E, Algın Yapar E, Garg M, Sood M, *et al.* Bioactive loaded novel nano-formulations for targeted drug delivery and their therapeutic potential. Pharmaceutics 2022;14:1091-1117.
100. Hema S, Thambiraj S, Shankaran DR. Nanoformulations for targeted drug delivery to prostate cancer: An overview. J Nanosci Nanotechnol 2018;18:5171-1591.
101. Waheed S, Li Z, Zhang F, Chiarini A, Armato U, Wu J. Engineering nano-drug biointerface to overcome biological barriers toward precision drug delivery. J Nanobiotechnol 2022;20:395-419.
102. Agrawal M, Saraf S, Saraf S, Dubey SK, Puri A, Patel RJ, *et al.* Recent strategies and advances in the fabrication of nano lipid carriers and their application towards brain targeting. J Control Release 2020;321:372-415.
103. Maher R, Moreno-Borrallo A, Jindal D, Mai BT, Ruiz-Hernandez E, Harkin A. Intranasal polymeric and lipid-based nanocarriers for CNS drug delivery. Pharmaceutics 2023;15:746-773.
104. Nguyen TT, Nguyen TTD, Tran N-M-A, Van Vo G. Lipid-based nanocarriers via nose-to-brain pathway for central nervous system disorders. Neurochem Res 2022; 47:552-573.
105. Deepika D, Dewangan HK, Maurya L, Singh S. Intranasal drug delivery of Frovatriptan succinate–loaded polymeric nanoparticles for brain targeting. J Pharmaceut Sci 2019;108:851-859.
106. Girotra P, Singh SK, Kumar G. Development of zolmitriptan loaded PLGA/poloxamer nanoparticles for migraine using quality by design approach. Int J Biolog Macromol 2016;85:92-101.
107. Dali P, Shende P. Self-assembled lipid polymer hybrid nanoparticles using combinational drugs for migraine via intranasal route. AAPS PharmSciTech 2022;24:20.
108. Bhanushali R, Gatne M, Gaikwad R, Bajaj A, Morde M. Nanoemulsion based intranasal delivery of antimigraine drugs for nose to brain targeting. Indian J Pharmaceut Sci 2009;71:707-709.
109. Harjot K, AM John N. Nanoemulsion for migraine prophylaxis nasal drug delivery: preparation, characterization and *in vitro* evaluation. Pharmaceut Nanotechnol 2016;4:229-241.
110. AMJ N, Harjot K. Flunarizine dihydrochloride nanoemulsion for migraine nasal drug delivery: fabrication, characterization and in vitro study. Drug Deliv Let 2016;6:104-112.
111. Divanbeigi N, Yousefian M, Etemad L, Azizi M, Ebrahimzadeh A, Oroojalian F, *et al.* Improving the anticancer efficiency of doxorubicin by luteolin nanoemulsion: *In vitro* study. Nanomed J 2023;10:47-58.
112. Abdou EM, Kandil SM, El Miniawy HM. Brain targeting efficiency of antimigrain drug loaded mucoadhesive intranasal nanoemulsion. Int J Pharmaceut 2017;529:667-677.
113. Honarvar NM, Soveid N, Abdolahi M, Djalali M, Hatami M,

Karzar NH. Anti-neuroinflammatory properties of n-3 fatty acids and nano-curcumin on migraine patients from cellular to clinical insight: a randomized, double-blind and placebo-controlled trial. Endocrine Metab Immun Dis Drug Target 2021;21:365-373.
114. Bulboacă AE, Bolboacă SD, Bulboacă AC, Porfire AS, Tefas LR, Suciu ŞM, *et al*. Liposomal curcumin enhances the effect of naproxen in a rat model of migraine. Med Sci Monit 2019; 25: 5087–5097.
115. Abdolahi M, Jafarieh A, Sarraf P, Sedighiyan M, Yousefi A, Tafakhori A, *et al*. The neuromodulatory effects of ω-3 fatty acids and nano-curcumin on the COX-2/iNOS network in migraines: A clinical trial study from gene expression to clinical symptoms. Endocrine Metab Immun Dis Drug Target 2019;19:874-884.
116. Jha S, Mishra D. Evaluation of brain targeting potential of zolmitriptan mucoadhesive nanoparticles for intranasal drug delivery. Pharmaceut Nanotechnol 2022;10:113-124.
117. Khezri FANZ, Lakshmi C, Bukka R, Nidhi M, Nargund SL. Pharmacokinetic study and brain tissue analysis of Zolmitriptan loaded chitosan nanoparticles in rats by LC-MS method. Int J Biolog Macromol 2020;142:52-62.
118. Kataria I, Shende P. Nose-to-brain lipid nanocarriers: An active transportation across BBB in migraine management. Chem Physic Lipid 2022;243: 105177.
119. Mandlik SK, Ranpise NS, Mohanty BS, Chaudhari PR. A coupled bimodal SPECT-CT imaging and brain kinetics studies of zolmitriptan-encapsulated nanostructured polymeric carriers. Drug Deliv Translat Res 2018;8:797-805.
120. Mohamed MI, Abdelbary AA, Kandil SM, Mahmoud TM. Preparation and evaluation of optimized zolmitriptan niosomal emulgel. Drug Develop Industr Pharm 2019;45:1157-1167.
121. Jain R, Nabar S, Dandekar P, Patravale V. Micellar nanocarriers: potential nose-to-brain delivery of zolmitriptan as novel migraine therapy. Pharmaceut Res 2010;27:655-664.
122. Awadeen RH, Boughdady MF, Meshali MM. Quality by design approach for preparation of zolmitriptan/chitosan nanostructured lipid carrier particles–formulation and pharmacodynamic assessment. Int J Nanomed 2020:8553-8568.
123. Hassan DH, Shohdy JN, El-Setouhy DA, El-Nabarawi M, Naguib MJ. Compritol-based nanostrucutured lipid carriers (NLCs) for augmentation of zolmitriptan bioavailability via the transdermal route: *In vitro* optimization, *ex vivo* permeation, in vivo pharmacokinetic study. Pharmaceutics 2022;14:1484-1505.
124. Abd El-Halim SM, Mamdouh MA, Eid SM, Ibrahim BM, Aly Labib DA, Soliman SM. The potential synergistic activity of zolmitriptan combined in new self-nanoemulsifying drug delivery systems: Atr-ftir real-time fast dissolution monitoring and pharmacodynamic assessment. Int J Nanomed 2021:6395-412.
125. Shelke S, Shahi S, Jalalpure S, Dhamecha D. Poloxamer 407-based intranasal thermoreversible gel of zolmitriptan-loaded nanoethosomes: Formulation, optimization, evaluation and permeation studies. J Liposome Res 2016;26:313-323.
126. Hansraj GP, Singh SK, Kumar P. Sumatriptan succinate loaded chitosan solid lipid nanoparticles for enhanced anti-migraine potential. Int J Biolog Macromol 2015;81:467-476.
127. Patravale VB, Upadhaya PG, Jain RD. Preparation and characterization of micelles. Methods Mol Biol 2019; 2000:19-29.
128. Masjedi M, Azadi A, Heidari R, Mohammadi-Samani S. Nose-to-brain delivery of sumatriptan-loaded nanostructured lipid carriers: preparation, optimization, characterization and pharmacokinetic evaluation. J Pharm Pharmacol 2020;72:1341- 1351.
129. Assadpour S, Akhtari J, Shiran MR. Pharmacokinetics study of chitosan-coated liposomes containing sumatriptan in the treatment of migraine. Caspian J Inter Med 2022;13:90-99.
130. Yadav RK, Shah K, Dewangan HK. Intranasal drug delivery of sumatriptan succinate-loaded polymeric solid lipid nanoparticles for brain targeting. Drug Develop Industr Pharm 2022;48:21-28.
131. Girotra P, Singh SK. A comparative study of orally delivered PBCA and ApoE coupled BSA nanoparticles for brain targeting of sumatriptan succinate in therapeutic management of migraine. Pharmaceut Res 2016;33:1682-1695.
132. Bulboacă AE, Bolboacă SD, Stănescu IC, Sfrângeu CA, Porfire A, Tefas L, *et al*. The effect of intravenous administration of liposomal curcumin in addition to sumatriptan treatment in an experimental migraine model in rats. Int J Nanomed 2018:3093-3103.
133. Ribeiro LN, Rodrigues da Silva GH, Couto VM, Castro SR, Breitkreitz MC, Martinez CS, *et al*. Functional hybrid nanoemulsions for sumatriptan intranasal delivery. Front Chem 2020;8:589503.
134. Berah R, Ghorbani M, Moghadamnia AA. Synthesis of a smart pH-responsive magnetic nanocomposite as high loading carrier of pharmaceutical agents. Int J Biolog Macromol 2017;99:731-738.
135. Girotra P, Thakur A, Kumar A, Singh S.K. Identification of multi-targeted anti-migraine potential of nystatin and development of its brain targeted chitosan nanoformulation. Int J Boil Macromol 2017;96:687–696.
136. Neha Gulati N, Upendra Nagaich U, Saraf SA. Intranasal delivery of chitosan nanoparticles for migraine therapy. Sci Pharm 2013; 81:843-854.
137. Abou Youssef NAH, Kassem AA, Farid RM, Ismail FA, Magda Abd Elsamea E-M, Boraie NA. A novel nasal almotriptan loaded solid lipid nanoparticles in mucoadhesive in situ gel formulation for brain targeting: Preparation, characterization and in vivo evaluation. Int J Pharmaceut 2018;548:609-624.
138. Salem LH, El-Feky GS, Fahmy RH, El Gazayerly ON, Abdelbary A. Coated lipidic nanoparticles as a new strategy for enhancing nose-to-brain delivery of a hydrophilic drug molecule. J Pharmaceut Sci 2020;109:2237-2251.
139. Abo El-Enin HA, Mostafa RE, Ahmed MF, Naguib IA, A. Abdelgawad M, Ghoneim MM, *et al*. Assessment of nasal-brain-targeting efficiency of new developed mucoadhesive emulsomes encapsulating an anti-migraine drug for effective treatment of one of the major psychiatric disorders symptoms. Pharmaceut 2022;14:410-427.
140. Girotra P, Singh SK. Multivariate optimization of rizatriptan benzoate-loaded solid lipid nanoparticles for brain targeting and migraine management. AAPS PharmSciTech 2017;18:517-528.
141. Dali P, Shende P. Use of 3D applicator for intranasal microneedle arrays for combinational therapy in migraine. Int J Pharmaceut 2023;635:122714.
142. Ita K, Ukaoma M. Progress in the transdermal delivery of antimigraine drugs. J Drug Deliv Sci Technol 2022;68:103064.
143. Chatterjee B, Gorain B, Mohananaidu K, Sengupta P, Mandal UK, Choudhury H. Targeted drug delivery to the brain via intranasal nanoemulsion: Available proof of concept and existing challenges. Int J Pharmaceut 2019;565:258-268.
144. Puri V, Nagpal M, Singh I, Singh M, Dhingra GA, Huanbutta K, *et al*. A comprehensive review on nutraceuticals: therapy support and formulation challenges. Nutrients 2022;14:4637-4664.
145. Chaurasiya S, Kulhari H. Essential Considerations for Brain Delivery of Nanoformulations. Drug Delivery Strategies in Neurological Disorders: Challenges and Opportunities: Springer; 2024. 251-269.
146. Chattopadhyay S, Das S, Sarma KN. Nose-to-brain drug delivery: An update to the alternative path to successful targeted antimigraine drugs. Int J Appl Pharm 2021;13:67-75.
147. Bahadur S, Pathak K. Challenges in Targeting Nasal Passage and Nose-to-Brain Delivery via Nanoemulsions. Nasal Drug Delivery: Formulations, Developments, Challenges, and Solutions 2023:59-82.
148. Bhunia S, Kolishetti N, Vashist A, Yndart Arias A, Brooks D, Nair M. Drug delivery to the brain: recent advances and unmet challenges. Pharmaceutics 2023;15:2658-2682.