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Review Article

A REVIEW OF TRIPTAN FORMULATIONS FOR THE TREATMENT OF MIGRAINE

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ABSTRACT

Migraine is a severe headache that induces throbbing and pounding pain all over the head and is accompanied by sensitivity towards light, sound and touch. Triptans is one of the major class used to treat migraine. These are mainly employed in treating acute migraine conditions. This review paper focuses on comprehensive analysis of triptan-based treatments for migraine, with an emphasis on creating new dosage forms that would improve bioavailability and therapeutic effectiveness. This paper includes pharmacokinetics, mechanism of action and ability to target trigeminocervical system of almotriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Innovative methods that have potential to boost medication transport to brain with less systemic exposure and quick relief from migraine symptoms are explained. It is finally concluded that triptan class is still a viable treatment option for migraine, with new dosage forms providing consistent therapeutic effect.

Keywords: Migraine, Triptan, Dosage form, Bioavailability, Method of preparation, Headache

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INTRODUCTION

Common primary headache disorders like migraine ranked sixth in terms of disability and was the top cause of neurological disability worldwide in 2015 [1]. Migraineurs endure excruciating headache pain that may last up to 72 h and are frequently accompanied by sensitivity towards light, sound, and touch [2]. There are two types of migraine treatment: Prophylactic (preventive) medication treatment and acute medication treatment for individual attacks [3]. The most prevalent neurological vascular headache condition, migraine headache, induces throbbing, pounding pain all over the head. It often involves inadequate arterial sensitivity in the brain, which sets off triggers that frequently cause abrupt changes in artery diameter this leads to the enlargement of arteries in the brain and scalp that causes severe headache pain [4]. Several medications available to target migraine have recently been developed. These include monoclonal antibodies that target CGRP receptor antagonists intended for absorptive use. These drugs mark a step forward in the management of migraine, providing target therapy based on established pathophysiological pathways [5].

The acute antimigraine medication triptan is a serotonergic agonist. With the release of sumatriptan 25 y ago, triptan drugs were initially authorized as absorptive medicines in the treatment of migraine headaches. Sumatriptan was first made available in Europe in 1991 the treatment of this cripping line, which affects millions of people worldwide, was completely transformed [6]. Six additional triptans have been introduced to the pharmacopeia since sumatriptan was prescribed in the US. The pharmacokinetics of triptans varies slightly, but they are all serotonergic agonists that act on 5-HT1b and 5-HT1d receptors. Although there is debate about a single triptan mechanism for preventing migraine, meningeal vasoconstriction, central trigeminocervical pathway regulation, and blocking the production of trigeminal vasoactive peptides seem to be involved [7].

- **Stage 1 Warning:** This stage can occur 48 h before an attack and is characterized by mood swings, irritability, depression, excessive thirst or appetite, sensitivity to light and sound, and frequent urination.
- **Stage 2 Aura:** An hour before the headache, this stage occurs. Visual abnormalities, disorientation, blind patches in eyesight, tingling in the skin, etc. are some of the symptoms.
- **Stage 3 Headache:** along with accompanying symptoms including nausea, vomiting, dizziness, blurred vision, loss of appetite, sensitivity to light, noise and odors, etc. this stage of headache lasts for approximately 4 to 72 h.
- **Stage 4 Postdrome:** The ache eventually disappears, but you can still feel exhausted, lethargic, and washed out [8].

The Gods of ancient Egypt, such as Horus said “My head, my head” and Thoth said, “The side of my side,” all experienced headaches. Incanations were also used to combat other migraine characteristics including nausea and anorexia. Hippocrates was the first to diagnose headaches as a real illness rather than a divine visitation, and he did so only in Ancient Greece when he distinguished between several kinds of headaches in his aphorisms. As a result, he was the first to describe several widely recognized characteristics of migraine, including the visual aura, the headache’s subsequent start, its generalization, and its alleviation by vomiting. Celcus (25 BC-50 AD) was the first person to describe migraine as a chronic, non-fatal illness with triggers and stress and stated that headache could be localized or widespread. Galen (AD 131-201) defined migraine as “a painful disorder affecting approximately one half of the head, either the right or left side, which extends along the length of longitudinal suture”. He was interested in the connections between the extracranial and intracranial because he believed that migraine was caused by toxic vapor that enter the brain from other parts of the body. For centuries the humoral theory identified four humors: blood, phlegm, black and yellow bile was prevalent. The yellow bile was linked to migraine vomiting [9].

Table 1: Types of treatment for migraine [10]

Acute treatment formulations	Preventive treatment formulations
1) Triptans (eg: sumatriptan, rizatriptan)	1) Beta-blockers (eg: Propranolol)
2) Ergotamines (eg: dihydroergotamine)	2) Anticonvulsants (eg: valproate)
3) Nonsteroidal anti-inflammatory drugs (NSAIDs) (eg: ibuprofen)	3) Antidepressants (eg: amitriptyline)
4) Anti-nausea medications (eg: metoclopramide, ondansetron)	4) Calcium channel blockers (eg: verapamil)

Different dosage forms available for the treatment of migraine

Almotriptan

It is the first medication licensed by the FDA to treat adult migraine headaches with or without aura. It is especially helpful for teenagers who have experienced untreated migraines lasting four hours or more in the past.

Mechanism of action: Almotriptan selectively binds to the cranial artery 5-HT1B and 5-HT1D serotonin receptor. Researchers believe that the process of relieving migraine involves neurogenic inflammation reduction, which is linked to the activation of 5-HT receptor.

Pharmacokinetics: Almotriptan reduces cerebral blood flow, constricts blood vessels in the brain, and restricts the pain impulses reaching the brain. The oral bioavailability is 69.1% and the half-life is about 3 h. It has low water solubility and therefore, ultimately affects bioavailability. Almotriptan is predominantly metabolized by cytochrome CYP450 and is eliminated through urine. It has a short plasma half-life and better oral bioavailability in contrast to prior-generation triptans like sumatriptan [11].

Table 2: Literature survey of almotriptan formulation as novel dosage form

Drug (Triptan)	Dosage form	Excipients	Method of preparation	Outcome
Almotriptan	Mucoadhesive microsphere	Almotriptan malate, Span-80, n-octanol, calcium chloride, gellan gum, distilled water, isopropyl alcohol	w/o crosslinking emulsification method	The microsphere nasal formulation improved mucosal residence time and dosing frequency was reduced [12].
	Mucoadhesive insitu nasal gel containing solid lipid nanoparticle	Almotriptan malate, glyceryl behenate, glyceryl palmitostearate, stearic acid, tween-80, agar, saline 0.9%, formaldehyde, dichloromethane, phospholipon 90 H, polyvinylalcohol, Poloxamer 407, carbopol 974p, Lubrizol, sodium alginate, sodium carboxy methyl cellulose, mucin, methanol, hematoxylin, eosin stain, ethyl acetate, diethyl ether, glacial acetic acid, benzalkonium chloride, total protein, sterile water	w/o/w double emulsion solvent evaporation method	Small particles led to increased absorption and the brain was successfully targeted through in situ nasal gel [13].
	Mucoadhesive buccal film	Almotriptan, Proloc 15, eudragit RL 100, eudragit RS 100, propylene glycol, polyvinylpyrrolidone, polyethylene glycol 400, methanol, ethyl cellulose, acetone, isopropyl alcohol, dibutyl phthalate.	Solvent casting method	Drug release, permeability, and therapeutic efficacy were improved [14].
	Mucoadhesive insitu nasal gel	Almotriptan malate, PF127, dialysis membrane, PF68, carboxymethyl chitosan, benzalkonium chloride.	Cold technique	Increased nasal residence time and fast onset of action are achieved [15].

Naratriptan

Mechanism of action: It is a selective agonist that acts on serotonin (5-HT1B and 5-HT1D) receptors in the cranial arteries; it constricts blood vessels and minimizes sterile inflammation that is associated with a drop in migraine pain.

Pharmacokinetics: Naratriptan is well absorbed, the volume of distribution is about 170L metabolized by the liver via CYP and 50% of the total dose in unchanged form; 30% of the total dose in the form of the metabolite is eliminated through urine [16].

Rizatriptan

Mechanism of action: Rizatriptan exhibits high affinity for the 5 HT1A site and low affinity for the non-5HT site. It is demonstrated that isolated middle meningeal arteries have a greater degree of cerebral selectivity than coronary arteries in people [20].

Pharmacokinetics: Rizatriptan is well absorbed when administered through the oral route, but the absolute oral bioavailability is reduced to 45% due to first-pass metabolism. The mean volume of distribution for male participants is 140L, while for females it is about 110L. Monoamine oxidase-A (MAO-A) is the primary enzyme that mediates the oxidative deamination of rizatriptan, resulting in the formulation of non-pharmacologically active triazolomethyl-indole-3-acetic acid. The pharmacological activity of N-monodesmethyl-rizatriptan, a minor metabolite, is equivalent to the parent drug. 14 % of the unchanged form of rizatriptan is excreted through urine and 51% through first pass metabolism [21].

Table 3: Literature survey of naratriptan formulation as novel dosage form

Drug (Triptan)	Dosage form	Excipients	Method of preparation	Outcome
Naratriptan	Fast disintegrating tablet	Naratriptan hydrochloride, glycine, mannitol, gelatin, amylose, soluble starch, dextrin, distilled deionized water	Lyophilization	To treat episodes of migraine, quick pain relief is preferred. Fast disintegrating tablet with good mechanical strength provides a high rate and extent of absorption and onset of action [17].
	Oral transmucosal delivery	Naratriptan HCL, ethanol, transcutol P, oleic acid, methocel 60 HG, PEG400, dipropylene glycol, miglyol, PEG 200, propylene glycol, phosphate buffer saline tablet, acetonitrile, trifluoroacetic acid, triethanolamine, methanol, water	The liquid dosage forms were prepared by dissolving a known amount of naratriptan base in the desired amount of solvent.	Transcutol permeation increases the uptake of naratriptan through the buccal membrane [18].
	Thermo reversible mucoadhesive in situ nasal gel	Naratriptan hydrochloride, poloxamer 407, carbopol 934, cellophane membrane	Cold technique	The addition of carbopol helps to improve the penetration of the drug and act as a mucoadhesive agent, whereas the poloxamer as a thermo-reversible agent helps to deliver a drug in a sustained manner [19].

Table 4: Literature survey of rizatriptan formulation as novel dosage form

Drug (Triptan)	Dosage form	Excipients	Method of preparation	Outcome
Rizatriptan	Mouth dissolving tablet	Rizatriptan benzoate, indion 234, indion 414, carboxymethylcellulose calcium, aspartame, mannitol, magnesium stearate, crospovidone, avicel pH-102	Direct compression method	A higher ratio of water absorption and released 99.60% of the drug in a 2 min 15 sec time frame [22].
	Fast-dissolving buccal film	Rizatriptan benzoate, maltodextrin, xanthan gum, gum karaya, cinnamon oil, mannitol, saccharin, starch, and citric acid.	Emulsion evaporation technique	The emulsion evaporation technique used to prepare disintegrating film was found to be more effective in treating migraine [23].
	Chitosan nanoparticle	Rizatriptan, chitosan, acetic acid, tripolyphosphate, mannitol.	Ionic gelation method	Chitosan nanoparticle resulted in an improved formulation that provides nasal drug delivery insights [24].
	Orodispersible electrospun	Rizatriptan benzoate, PVA, PVP (K60), PVP (K30), PVP (K90)	Electrospinning and casting method	Electrospun orodispersible film was found to improve bioavailability and effective delivery for treating migraine [25].
	Mucoadhesive buccal film	Rizatriptan benzoate, HPMC K4M, PVA, polyethylene oxide, glycerol, disodium hydrogen phosphate, sodium chloride, potassium chloride, potassium dihydrogen phosphate, magnesium chloride, sodium hydrogen carbonate, HCL, calcium chloride, phosphate buffer saline	Solvent casting method	The mucoadhesive buccal film was found to be effective delivery for the treatment of migraine due to uniform drug release [26].
	Insitu nasal gel	Rizatriptan, carbopol 934P, HPMC (various grades), PEG400	Cold technique	In situ nasal gel formulation proved to improve bioavailability as compared to oral route [27].
	Intranasal spray formulation	Rizatriptan benzoate, rizatriptan base, trifluroacetic acid, acetonitrile, propylene glycol, PEG400, NF, edetate disodium, dehydrated alcohol, benzalkonium chloride, anhydrous citric acid, butylated hydroxyl anisole, methyl paraben, propyl paraben, HCL, NaOH	This method employs the preparation of two phases: the water phase and the ethanol phase.	Quick onset of action was achieved [28].

Table 5: Literature survey of sumatriptan formulation as novel dosage form

Drug (Triptan)	Dosage form	Excipients	Method of preparation	Outcome
Sumatriptan	Chitosan-coated liposome containing sumatriptan	Hydrogenated soya phosphatidyl-choline, acetonitrile, methanol, ethyl acetate, sodium phosphate, formic acid, sodium hydroxide, chitosan, and sumatriptan.	Thin film hydration method	The nanoliposome containing sumatriptan was found to be sale and improved bioavailability was noted [30].
	Sumatriptan intrarectal mucoadhesive gel	Sumatriptan, poloxamer 407, poloxamer 188, xyloglucan, sodium hydroxide, potassium dihydrogen phosphate, benzalkonium chloride.	Thin film hydration method	The nanoliposome containing sumatriptan was found to be sale and improved bioavailability was noted [31].
	Transdermal sumatriptan microneedle system	Sumatriptan succinate, polyvinylpyrrolidone, glycerine, polysorbate 80, nitrazine yellow	Ionic complexation was used to formulate complex nasal inserts by electrostatic interaction.	Microneedle administration method offers an affordable substitute with no unfavorable side effects [32].
	Freeze-dried nasal inserts	Sumatriptan succinate, chitosan, carrageenan, mannitol	Solvent diffusion evaporation technique	The inserts were found to be effective because uptake of water made them viscous thereby leading to electrostatic interaction and further release of the drug in a controlled manner [33].
	Nanostructure lipid carrier loaded with sumatriptan	Sumatriptan, acetone, stearic acid, Brij 35, Brij 72, triolein, cholesterol, deionized water, sodium hydroxide, ammonium acetate, glacial acetic acid, ethyl acetate, acetonitrile	Freeze drying technology	The drug delivery to the brain to treat migraine was found to be effective and provides fast relief [34].
	Orodispersible tablet	Sumatriptan succinate, gelatin, plasdone K90D, sorbitol, sucrose, potassium dihydrogen orthophosphate, sodium hydroxide, mannitol, disodium ethylene diamine tetra acetic acid, magnesium stearate, methanol, camphor, xanthan gum, glycine SR, sucralose, distilled water.	AVP-825 breath-powered exhalation device	The orodispersible tablet was found to be fast disintegration and dissolution and provide a fast onset of action [35].
	Sustained release of Mucoadhesive buccal film	Sumatriptan succinate, HPMC, PEG, xanthan gum, potassium persulphate, acrylamide, acetone	Solvent casting method and emulsion solvent diffusion	Mucoadhesive films are an excellent alternative for delivering medication in a sustained manner and avoid first pass metabolism [36].
	Dry nasal powder of sumatriptan	Sumatriptan, lactose	Breath powder exhalation device	It was demonstrated that formulation was found to have fast onset, absorption, and low systemic exposure [37].
	Mucoadhesive buccal disc and sublingual film	Sumatriptan succinate, metoclopramide hydrochloride, HPMC (E-15), ethanol, dichloromethane, potassium dihydrogen phosphate, Sodium chloride, potassium chloride, sodium sulfate, ammonium acetate, urea, lactic acid, liquid paraffin, span 80 and propylene glycol	Emulsion solvent diffusion and solvent casting method	Mucoadhesive film and disc were found to have improved the release of drug and enhanced mucoadhesive characteristics [38].
	Sumatriptan succinate insitu nasal gel	Sumatriptan succinate, polyvinyl pyrolide, poloxamer, carbomer, benzalkonium chloride	Cold technique	Nasal residence time was improved, led to prolonged release of drug [39].
	Fast-dissolving oral dosage form as a tablet and oral film	Sumatriptan succinate, hydroxyl propyl methyl cellulose (K100M), urad dal, polyvinyl alcohol, soluplus, propylene glycol, ethanol, mannitol, citric acid water	The orally disintegrating tablet was prepared by wet granulation technique and the oral film was prepared by solvent casting method.	The addition of mucilage in an orally disintegrating tablet and a combination of HPMC K100M and soluplus helps to improve disintegration, and the maximum amount of drug release within a short time [40].

Sumatriptan

Mechanism of action: Sumatriptan reduces neurogenic inflammation by vasoconstriction of large cerebral blood vessels, inhibits transmission through peripheral neuronal inhibition, and reduces pain from migraines and their accompanying symptoms by inhibiting the activity of second-order neurons in the trigeminal cervical complex.

Pharmacokinetics: sumatriptan has 14% of bioavailability and the volume of distribution is about 17L. The inactive indoleacetic analogue of sumatriptan is produced after metabolism and is mainly excreted through urine and feces [29].

Zolmitriptan

Mechanism of action: Through direct 5-HT1B mediated cerebral blood vessel dilation as well as 5-HT1D mediated reduction of CGRP release, triptans can improve vasoconstriction.

Pharmacokinetics: Zolmitriptan has fast absorption across nasal mucosa; the volume of distribution is about 7-8 l/kg, metabolized by the liver by cyp450 and eliminated through urine and feces [41].

Table 6: Literature survey of zolmitriptan formulation as novel dosage form

Drug (Triptan)	Dosage form	Excipients	Method of preparation	Outcome
Zolmitriptan	Insitu mucoadhesive intranasal gel	Zolmitriptan, ketorolac tromethamine, tamarind gum, pluronic F127, polyethylene glycol, potassium dihydrogen orthophosphate, acetonitrile, trimethylamine, orthophosphoric acid, sodium chloride.	Mix polymer with a gelling agent followed by the addition of water and additives.	Improves bioavailability and nasal residence time [42].
	Zolmitriptan-loaded bilosome that are incorporated in insitu nasal gel.	Zolmitriptan, brij35, brijO10, cholesterol, hydroxypropyl methylcellulose, poloxamer 407, sodium deoxycholate, span 20, span 40, span 60, span 80, tween 65, tween 80, dialysis tubing cellulose membrane, methylene blue, normal saline, acetonitrile, formic acid, torsemide, distilled de-ionized water.	The thin film hydration method was used for the preparation of bilosomes and the mucoadhesive gel was prepared by cold method.	A mucoadhesive gel containing bilosome with drug loaded in it was found to be effective for brain targeting and ultimately, the bioavailability was also enhanced [43].
	Zolmitriptan intranasal spanlastics	Zolmitriptan, span60, tween 80, ethanol	Ethanol injection method	Zolmitriptan was found to be effective in brain targeting [44].

CONCLUSION

It was concluded that the triptan class was found to be effective in treating migraine as its loading in novel dosage form led to improve bioavailability and therapeutic efficacy when administered through various routes. Novel approaches will help to enhance patient compliance and efficiency.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Authors declare that we have no conflict of interest.

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