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Review Article

Beyond Oral Triptans: Exploring Herbal Inhalers and Pulmonary Delivery Systems for Fast-Acting Migraine Relief

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Migraine is a leading cause of global neurological disability, characterized by recurrent, severe headache attacks that demand rapid and effective abortive intervention. While conventional treatments rely heavily on oral triptans, these formulations often suffer from delayed clinical onset, extensive hepatic first-pass metabolism, and reduced absorption due to migraine-associated nausea and gastroparesis. Pulmonary drug delivery offers a compelling non-invasive alternative, providing rapid systemic drug absorption across the vast alveolar surface area while avoiding gastrointestinal degradation. This review explores the paradigm shift "beyond oral triptans," focusing on the development, phytochemistry, and engineering of herbal inhalation systems for fast-acting migraine relief. The manuscript details the neurobiological mechanisms underlying migraine attacks—spanning hypothalamic initiation, cortical spreading depression (CSD), trigeminovascular system (TGVS) activation, and the release of key vasoactive neuropeptides such as CGRP and PACAP. It evaluates conventional and novel triptan delivery systems alongside a comprehensive analysis of over 30 standardized phytomedicines (including Tanacetum parthenium, Petasites hybridus, Zingiber officinale, Mentha piperita, and Lavandula angustifolia). Their bioactive phytoconstituents and distinct pharmacological mechanisms—such as 5-HT receptor agonism, CGRP suppression, TRPM8 activation, and inhibition of cyclooxygenase/lipoxygenase pathways—are systematically categorized. Furthermore, the review establishes a standardized pharmaceutical methodology for formulating herbal pressurized metered-dose inhalers (pMDIs). It outlines the utilization of eco-friendly hydrofluoroalkane propellants, jet-mill micronization to achieve respirable particle dimensions (d90 < 5.0 µm), and pressure-filling production methods. Essential in vitro characterization protocols—including Delivered Dose Uniformity (DDU), Aerodynamic Particle Size Distribution (APSD) using a Next Generation Impactor (NGI), spray pattern laser imaging, and container leakage testing—are detailed to guarantee reliable pulmonary deposition. Herbal pMDIs represent a novel, safe, and fast-acting therapeutic platform that bridges traditional phytotherapy with advanced aerosol drug delivery science.

Keywords: Migraine, Triptans, Herbal Inhaler, Pressurized Metered-Dose Inhaler (pMDI), Pulmonary Delivery.

INTRODUCTION

Migraine is the most frequently encountered neurological disorder in primary healthcare. According to the Global Burden of Disease study, migraine ranks as the second leading cause of disability worldwide and is the leading cause of disability among young women [1]. It is a persistent condition affecting approximately 18% of women and 6% of men globally, with chronic migraine impacting about 2% of the population [2]. Migraine is primarily a chronic headache disorder characterized by recurrent attacks lasting between 4 to 72 hours. These attacks are typically moderate to severe in intensity,

often triggered by routine physical activity, and commonly accompanied by symptoms such as nausea, vomiting, and photophobia [3]. Essential oils, which are complex mixtures of organic compounds responsible for their distinctive fragrances and biological activities, are widely used in various forms including inhalation, topical application, and ingestion [4–6]. Various extraction techniques are employed to obtain essential oils, which possess a broad spectrum of pharmacological properties, including antibacterial, antiviral, antifungal, and anti-inflammatory effects. These oils are also effective in managing psychological disorders by reducing anxiety and stress levels. Consequently, they are commonly used in aromatherapy, massage therapy, and as natural insect repellents. Essential oils are concentrated plant extracts with unique chemical compositions that provide therapeutic benefits across multiple industries, such as healthcare and beauty [7–8]. Specific oils like lavender, peppermint, tea tree, and eucalyptus exhibit diverse effects on stress reduction, anxiety relief, mental clarity, and concentration. Eucalyptus oil, in particular, is known for its effectiveness in treating respiratory conditions. Aromatherapy with essential oils is widely practiced to promote both physical and emotional well-being. For optimal results, proper usage and high-quality essential oils are essential [10–13].

Phathophysiology of migraine: steps are given blow.

1. Premonitory Phase & Hypothalamic Initiation

Before head pain develops, premonitory symptoms (such as fatigue, food cravings, mood alterations, and frequent yawning) signal early central nervous system dysfunction.

- **Hypothalamic Dysfunction:** Functional neuroimaging shows heightened activation in the hypothalamus and brainstem nuclei—including the periaqueductal gray (PAG) and locus coeruleus—prior to pain onset.

- **Disrupted Homeostasis:** The hypothalamus acts as a key integrator of circadian rhythms, stress responses, and endocrine signaling, rendering susceptible individuals vulnerable to internal and external migraine triggers [14].

2. Cortical Spreading Depression (CSD) & Aura

Cortical Spreading Depression (CSD) is the electrophysiological substrate responsible for the migraine aura.

- **Mechanism:** CSD is a slowly propagating wave (2–6 mm/min) of strong neuronal and glial cell depolarization across the cerebral cortex, followed by a prolonged period of neural suppression (Hill et al., 2024).

- **Ionic Shift & Chemical Release:** CSD causes massive efflux of intracellular potassium (K^+) and influx of sodium (Na^+) and calcium (Ca^{2+}), accompanied by extracellular release of glutamate, ATP, and nitric oxide.

- **Nociceptive Trigger:** The local metabolic and chemical cascade generated by CSD diffuses through the meninges to stimulate and sensitize primary nociceptive afferents of the trigeminal nerve [14].

3. Trigeminovascular System (TGVS) Activation

The core generator of throbbing headache pain is the **trigeminovascular system (TGVS)**, composed of primary sensory neurons originating in the trigeminal ganglion that innervate the cranial dura mater and perivascular cerebral blood vessels [15].

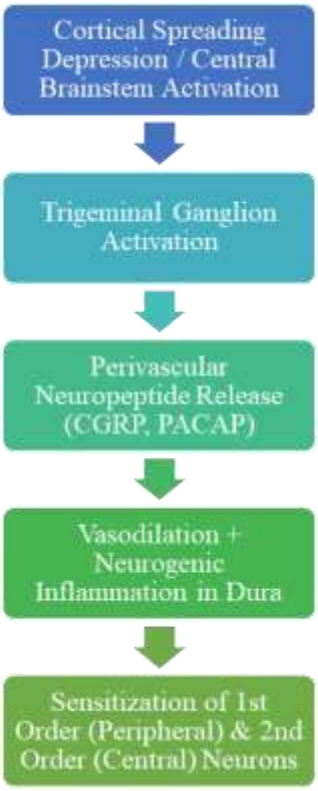

Figure 1: Steps of Phathophysiology of migraine

- **Neuropeptide Release:** Upon activation, trigeminal nerve terminals release key vasoactive peptides, primarily **Calcitonin Gene-Related Peptide (CGRP)** and **Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)** [16].

- **Neurogenic Inflammation:** CGRP and PACAP bind to GPCR receptors on vascular smooth muscle and mast cells, causing potent arterial vasodilation, mast cell degranulation, plasma protein extravasation, and local tissue edema.

4. Peripheral and Central Sensitization

- **Peripheral Sensitization:** Repeated exposure of dural nociceptors to inflammatory mediators lowers their activation threshold. Primary afferent neurons begin firing in response to normal arterial pulsations, producing the characteristic throbbing, pulsating headache [15].

- **Central Sensitization:** Continuous nociceptive input from the dura projects to second-order neurons in the **trigeminal** nucleus caudalis (TNC) within the brainstem. Over time, TNC neurons become hyperexcitable, expanding their receptive fields. This manifests clinically as cutaneous allodynia—where non-painful stimuli (such as touching the scalp or wearing glasses) feel painful [15].

Types of Migraine:

1. **Migraine with Aura (Complicated Migraine):**

   a. About 15% to 20% of migraine sufferers experience an aura.

   b. Aura consists of neurological symptoms such as visual disturbances that occur before the headache phase[17].

2. **Migraine without Aura (Common Migraine):**

   a. This type occurs without the aura phase.

   b. Symptoms during the headache phase are similar to those in migraine with aura, but the aura does not occur[17].

3. **Migraine without Head Pain (Silent or Acephalgic Migraine):**

a. Characterized by the presence of aura symptoms without the headache that typically follows [17].

4. Hemiplegic Migraine:

a. Causes temporary paralysis (hemiplegia) or neurological/sensory changes on one side of the body.

b. May include numbness, weakness, tingling, lack of sensation, dizziness, or vision problems.

c. Headache may or may not accompany these symptoms [18].

5. Retinal Migraine (Ocular Migraine):

a. Dull aching pain behind one eye that may spread to the head.

b. Temporary, partial, or complete loss of vision in the affected eye lasting from seconds to months.

c. Should be promptly evaluated by a healthcare professional as it may indicate a more serious condition. [17].

6. Chronic Migraine:

a. Defined as migraine occurring at least 15 days per month. [19].

b. The intensity and symptoms can vary.

c. Frequent use of pain relievers (more than 10-15 days per month) may worsen headache frequency. [20].

7. Migraine with Brainstem Aura:

a. Symptoms such as vertigo, slurred speech, double vision, or loss of balance precede the headache.

b. Headache pain often affects the back of the head.

c. May also include sudden onset of difficulty speaking, ringing in the ears, and vomiting. [17].

8. Status Migrainosus:

a. A rare, severe migraine lasting up to 72 hours.

b. Characterized by excruciating headache pain and nausea.

c. Can be triggered by certain medications or withdrawal from medication. [21].

Risk factors for migraines:

Over 38 million Americans get headaches, according to the American Migraine Foundation. There are a few things that could make you more likely to have them:

1] Sex: Women are three times as likely than men to experience migraines.

2] Age: Most adults between the ages of 10 and 40 experience migraine headaches. Around the age of 50, however, many women discover that their migraines either become better or go away.

3] Family History: Four out of five migraineurs have a family member with migraines. There is a 50% chance that a child may get identical headaches if one parent has previously experienced them. If both parents have them, the likelihood rises to 75% [17].

Table 1: Preparation used for the treatment of migraine

Sr. No.	Dosage form	Excipients used	Method of preparation	Reference
1.	Mucoadhesive microsphere	Almotriptan-malate span-80, n-octanol calcium-chloride, gellan, isopropyl alcohol	W/o crosslinking emulsification method	22
2.	Mucoadhesive insitu nasal get containing solid	Almotriptan malate, glyceryl behenate, glyceryl	w/o/w double emulsion solvent evaporation method	23

	lipid nanoparticle	Palmitostearate, stearic acid, tween-80, agar,saline 0.9%,formaldehyde ,dicholromrthane, phospholipon H 90, polyvinylalcohol, Poloxamer 407, Carbopol 974p, Lubrizol, sodium alginate, sodium carboxyv, methyl cellulose, mucin, methanol, Hematoxylin, eosin stain, ethyl-acetate, diethyl ether, glacial Acetic acid, Benzalkonium chloride, total protein Sterile water		
3.	Mucoadhesive buccal fiim	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	24
4.	Mucoadhesive membrane insitu nasal gel	Almotriptan malate, PF127, dialysis, PF68 carboxymethyl chitosan, benzalkonium chloride	Cold technique	25
5.	Fast disintegrating tablet	Naratriptan hydrochloride, glycine, mannitol, gelatin, amylose, soluble starch, dextrin, distilled deionized water.	Lyophilization	26
6.	Fast-dissolving buccal film	Rizatriptan benzoate, maltodextrin, xanthan gum, gum karaya, cinnamon oil, mannitol, saccharin, starch, and citric acid.	Emulsion evaporation technique	27
7.	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.	28
8.	Thermo reversible mucoadhesive in situ nasal gel	Naratriptan hydrochloride, poloxamer 407, carbopol 934, cellophane membrane	Cold technique	29
9.	Mouth dissolving tablet	Rizatriptan benzoate, indion 234, indion 414, carboxymethylcellulose calcium, aspartame, mannitol, magnesium stearate, crospovidone, avicel pH-102	Direct compression method	30
10.	Chitosan nanoparticl	Rizatriptan, chitosan, acetic acid, tripolyphosphate, mannitol.	Ionic gelation method	31
11.	Orodispersible electrospun	Rizatriptan benzoate, PVA, PVP (K60), PVP (K30), PVP (K90)	Electrospinning and casting method	32
12.	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	33
13.	Insitu nasal gel	Rizatriptan, carbopol 934P, HPMC (various grades), PEG400	Cold technique	34
14.	Intranasal spray formulation	Rizatriptan benzoate, rizatriptan base, trifluroacetic acid, acetonitrile, propylene	This method employs the preparation of two	35

		glycol, PEG400, NF, edetate disodium, dehydrated alcohol, benzalkonium chloride, anhydrous citric acid, butylated hydroxyl anisole, methyl paraben, propyl paraben, HCL, NaOH	phases: the water phase and the ethanol phase.	
15.	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	36
16.	Sumatriptan intrarectal mucoadhesive gel	Potassium dihydrogen phosphate, benzalkonium chloride, Sumatriptan, Sodium hydroxide, poloxamer 407, poloxamer 188, xyloglucan	Thin film hydration method	37
17.	Transdermal sumatriptan microneedle system	Sumatriptan succinate, polyvinylpyrrolidone, glycerine, polysorbate 80, nitrazine yellow	Ionic complexation was used to formulate complex nasal inserts by electrostatic interaction	38
18.	Freeze-dried nasal inserts	Sumatriptan succinate, chitosan, carrageenan, mannitol	Solvent diffusion evaporation technique	39
19.	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	40
20.	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	41
21.	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	42
22.	Sumatriptan succinate insitu nasal gel	Sumatriptan succinate, polyvinyl pyrolide, poloxamer, carbomer, benzalkonium chloride	Cold technique	43
23.	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	44
24.	Sustained release of Mucoadhesive buccal film	Sumatriptan succinate, HPMC, PEG, xanthan gum, potassium persulphate, acrylamide, acetone	Solvent casting method and emulsion solvent diffusion	45
25.	Dry nasal powder of sumatriptan	Sumatriptan, lactose	Breath powder exhalation device	46

26.	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.	47
27.	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.	48

Pharmaceutical Inhalers:

Pharmaceutical inhalers are specialized drug delivery systems designed to aerosolize therapeutic agents for direct administration to the lower respiratory tract. Pulmonary administration offers distinct pharmacokinetic advantages, including a rapid onset of action due to the vast alveolar surface area (approx 100 m^2) and thin epithelial barrier (0.2 - 0.7mcm), bypass of hepatic first-pass metabolism, and a reduction in systemic adverse effects compared to oral or parenteral routes [49-50].

1. Biopharmaceutical Principles & Deposition Mechanisms

The clinical efficacy of an inhaled formulation depends on the site of particle or droplet deposition within the respiratory tract, which is primarily governed by the **Mass Median Aerodynamic Diameter (MMAD)** and the patient's breathing pattern [50].

Deposition occurs through three main physical mechanisms:

- **Inertial Impaction:** High-velocity or larger particles fail to navigate the geometric turns of the upper respiratory tract. They impact on the mucosal walls of the oropharynx, larynx, and major bifurcations of the trachea, leading to swallowing and potential systemic absorption or local side effects.
- **Gravitational Sedimentation:** Known as the **respirable range**, these particles travel beyond the upper airways into the small bronchi and bronchioles, settling onto the airway epithelium under the influence of gravity during breath-holding.
- **Brownian Motion / Diffusion:** Sub-micron particles remain suspended in the air stream due to random collision with gas molecules and are predominantly exhaled before contacting alveolar walls [50].

Type of inhalers:

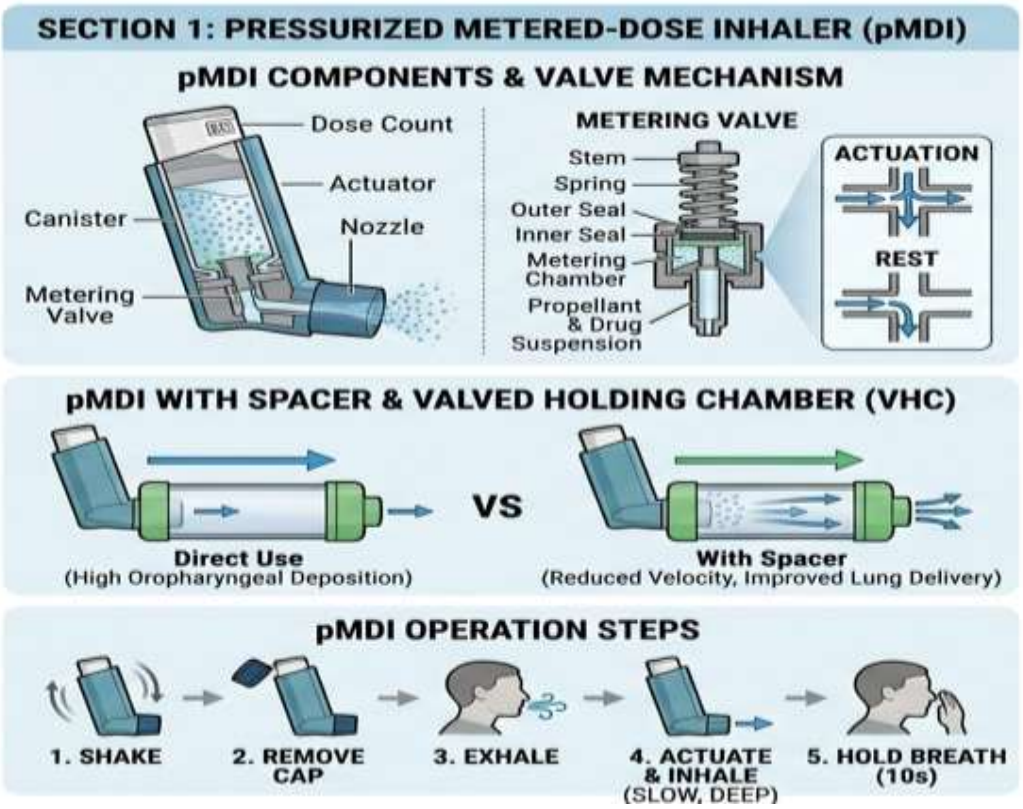

Figure 2: Pressure Metered Dose Inhaler [51].

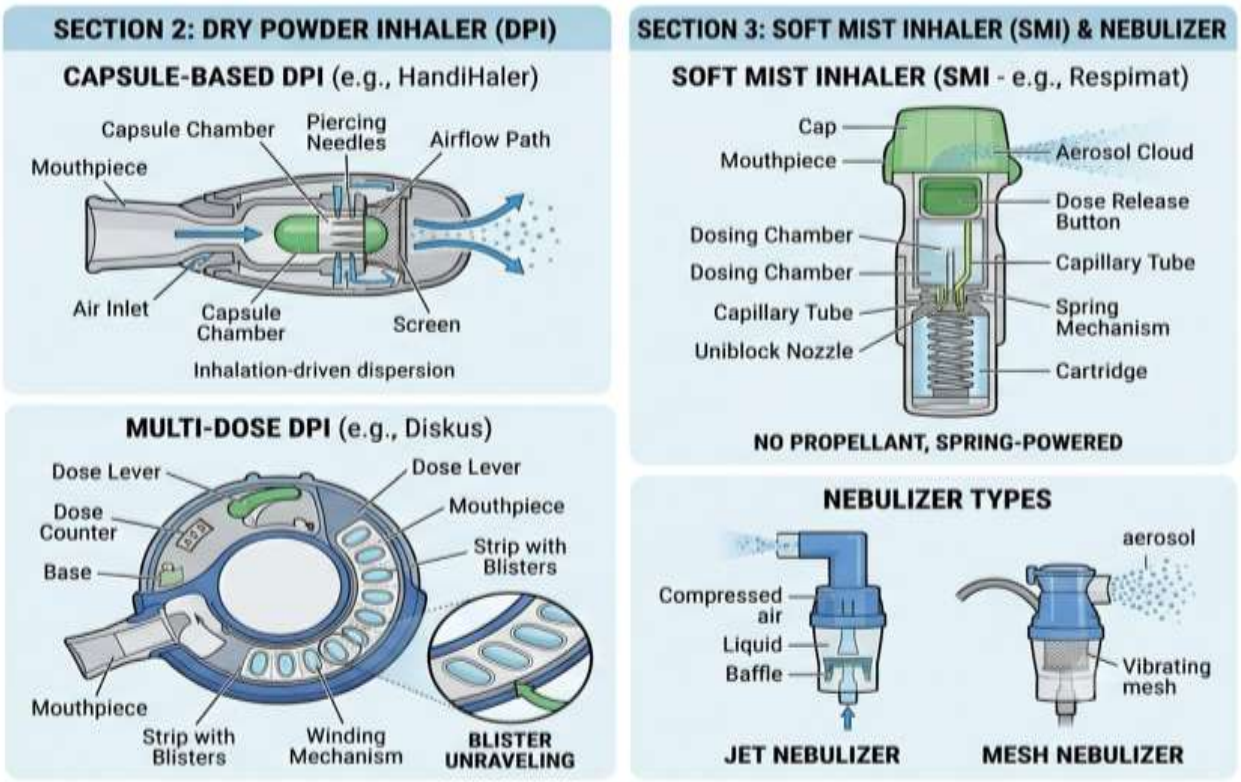

Figure 3: Dry powder Inhaler, Soft Mist Inhaler and Nebulizer [51].

Classification and comprehensive description of herbal inhalers

Herbal inhalers are non-invasive, volatile drug delivery systems designed to administer active

botanical constituents directly to the respiratory epithelium via the nasal pathway. The volatile essential oils and phytochemicals present in these devices act locally on the nasal mucosa and can exert systemic or central nervous system effects via olfactory absorption. Herbal inhalers are primarily classified into categories based on Composition and Use [52].

1. Classification Based on Composition

This classification differentiates inhalers based on the number of botanical active pharmaceutical ingredients (APIs) incorporated into the formulation.

a. Single Herbal Inhaler

- **Description:** A single herbal inhaler contains active volatile extracts, essential oils, or isolated pure phytoconstituents derived from a **single plant species**. The formulation relies exclusively on the pharmacological actions of one botanical source to achieve its targeted therapeutic effect [52].
- **Mechanism & Characteristics:**
    - Offers simplified quality control, standardization, and marker-based quantification (e.g., GC-MS profile of a single plant oil).
    - Reduced risk of unpredictable phytochemical interactions or complex matrix incompatibilities.
- **Examples:**
    - **Eucalyptus-only Inhaler:** Utilizing pure *Eucalyptus globulus* essential oil (rich in 1,8-cineole) for mucolytic and bronchodilatory activity.
    - **Menthol Inhaler:** Incorporating pure crystalline menthol derived from *Mentha arvensis* to trigger TRPM8 cold-receptors in the nasal passages [52-53].

b. Polyherbal Inhaler

- **Description:** A polyherbal inhaler integrates a formulation of **two or more plant-derived active substances**, essential oils, or aromatic constituents combined in precise ratios.
- **Mechanism & Characteristics:**
    - Leverages the concept of **synergy**, where multiple phytoconstituents work concurrently across different therapeutic pathways to enhance overall efficacy.
    - Allows lower individual concentration requirements for each ingredient, thereby reducing potential localized mucosal irritation.
- **Examples:**
    - Combined formulations containing **Menthol** (*Mentha arvensis*), **Camphor** (*Cinnamomum camphora*), **Thymol** (*Thymus vulgaris*), and **Eucalyptus oil** absorbed into a central carrier wick [53-54].

2. Classification Based on Use

This classification categorizes herbal inhalers based on their primary intended clinical application or therapeutic objective.

a. Decongestant Inhaler

- **Description:** Formulated specifically to relieve upper respiratory tract symptoms, including nasal congestion, rhinitis, sinusitis, and blocked nasal passages caused by infections or allergies [53].
- **Mechanism of Action:**
    - Active volatile monoterpenes (such as camphor, menthol, and cineole) stimulate cold-sensitive nerve endings (TRPM8 receptors) in the nasal mucosa, producing a physiological sensation of increased airflow and coolness.
    - They possess mild anti-inflammatory, antimicrobial, and secretolytic activities that help reduce mucosal swelling and facilitate mucus drainage [52].

- **Common Constituents:** Camphor, Eucalyptus Oil, Menthol, Thymol, Clove Oil, and Peppermint Oil [52].

b. Aromatherapy Inhaler

- **Description:** Designed primarily for systemic psychological, cognitive, and physiological benefits via olfactory stimulation rather than purely mechanical airway decongestion [54].
- **Mechanism of Action:**
    - Inhaled volatile aromatic molecules bind to olfactory receptor neurons in the nasal cavity.
    - The signals are transmitted directly via the olfactory bulb to the **limbic system** (the brain's emotional and memory center) and the central nervous system, modulating neurotransmitter release (e.g., serotonin, GABA) to promote stress reduction, alertness, or mood enhancement
- **Common Constituents:** Lavender Oil (*Lavandula angustifolia* for relaxation/anxiety), Brahmi (*Bacopa monnieri* for focus), Tulsi (*Ocimum sanctum*), and Lemon/Citrus oils (for fatigue and alertness) [52-54].

Figure 4: Advantages of Herbal Inhaler

MATERIALS AND METHODS

MATERIALS

- **Active Herbal Ingredients:** Standardized herbal extracts or purified bioactive phytoconstituents (e.g., Parthenolide, Menthol, Gingerols, or Linalool; purity >98%) [55,56].
- **Propellant:** Hydrofluoroalkane-134a (HFA-134a; 1,1,1,2-tetrafluoroethane) or HFA-227ea (pharmaceutical grade) [57,58].
- **Cosolvent:** Dehydrated Ethanol (USP/EP grade, >99.9% purity) used as a solubilizing agent for lipophilic herbal compounds [58,59].
- **Surfactants & Stabilizers:** Oleic acid (USP), Polyethylene glycol 400 (PEG 400), or Soy Lecithin (used to stabilize suspensions and lubricate valve mechanics) [59,60].
- **Container Closure System:** Anodized or fluoropolymer-coated aluminum canisters (10 mL capacity), metering valves (50 µL volume) with

fluorocarbon gaskets, and polypropylene actuators with a nozzle orifice diameter of 0.30 mm [60].

Table 2 Phytomedicine mechanisms of action in migraine

Sr. No.	Phytomedicine	Active component	Putative mechanism of action in migraine	Reference
1	Feverfew (*Tanacetum parthenium*)	Chrysanthenyl acetate, Tanetin	Inhibition of prostaglandin synthetase. Anti-inflammatory via inhibiting generation of pro-inflammatory eicosanoids.	61
2	Butterbur (*Petasites hybridus*)	Petasin, Isopetasin	Inhibition of leukotriene synthesis in leukocytes. Inhibition of voltage-sensitive calcium channels in arterial smooth muscle cells. Inhibition of mast cell degranulation, activation of TRPA1 channels. Dose-dependent inhibition of COX-2 mediated prostaglandin E2 release in rat microglia.	62
3	Cannabis (*Cannabis spp.*)	Cannabinoids (substituted meroterpenes)	Delta-9-THC inhibits release of serotonin from normal platelets. Cannabidiol is a lipoxygenase inhibitor that stimulates the release of prostaglandin E2 and inhibits leukotriene B4 synthesis *in vitro*. Endocannabinoid (AEA) inhibits neurogenic dural vasodilation mediated by CGRP and NO.	63
4	Saint John's Wort (*Hypericum perforatum*)	Hypericin	Counteracts NO donor-induced pain hypersensitivity and meningeal activation by blocking protein kinase C-mediated pathways involving NF-κB, CREB, STAT1.	64
5	Damask rose (*Rosa damascena*)	Flavonoids, Terpenes	Analgesic and anti-inflammatory properties, exact mechanism of action unknown.	65
6	Peppermint (*Mentha piperita*)	Menthol	TRPM8 activation with menthol reverses reduced facial pain thresholds induced by meningealinflammation.	66
7	Ginger (*Zingiber officinale*)	Gingerols, Shogaols, Zerumbone	Dual inhibition of COX-1/COX-2 and lipoxygenase (LOX) pathways; 5-HT1A/1B receptor agonist activity; 5-HT3 receptor antagonism reducing migraine-associated nausea; inhibition of CGRP release.	67
8	Ginkgo (*Ginkgo biloba*)	Ginkgolide B, Bilobalide	Inhibition of platelet-activating factor (PAF); attenuation of glutamate-mediated excitatory neurotransmission; suppression of cortical spreading depression (CSD); antioxidant vascular protection.	68
9	Lavender (*Lavandula angustifolia*)	Linalool, Linalyl acetate	Modulation of central GABAergic neurotransmission; reduction of autonomic nervous system hyperreactivity; suppression of neurogenic inflammation and voltage-gated calcium channels.	69
10	Turmeric (*Curcuma longa*)	Curcumin	Downregulation of NF-κB signaling; suppression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6); inhibition of COX-2 and neurogenic CGRP release.	70
11	Willow Bark (*Salix alba*)	Salicin (salicylic acid precursor)	Non-selective inhibition of cyclooxygenase (COX-1/COX-2) enzymes; suppression of inflammatory prostaglandin synthesis and central/peripheral pain sensitization.	71
12	Cayenne Pepper (*Capsicum annuum*)	Capsaicin	Desensitization of sensory nerve TRPV1 receptors; depletion of Substance P and neuropeptides from trigeminal ganglion nociceptive afferents.	72

13	Chamomile (*Matricaria chamomilla*)	Apigenin, Chamazulene, Bisabolol	Positive allosteric modulation of GABA-A receptors; downregulation of inducible nitric oxide synthase (iNOS) and COX-2 expressions.	73
14	Valerian (*Valeriana officinalis*)	Valerenic acid, Valepotriates	Potentiation of GABAergic tone via inhibition of GABA degradation and reuptake; central antispasmodic and sedative effects mitigating stress-induced migraine.	74
15	Coriander (*Coriandrum sativum*)	Linalool, Geraniol	Central antinociceptive and antioxidant properties; inhibition of nitric oxide synthase activity and scavenging of neurotoxic ROS.	75
16	Sweet Basil (*Ocimum basilicum*)	Linalool, Eugenol, Estragole	Modulation of peripheral nociceptors and blockade of inflammatory cascades; central analgesic interaction with opioid and GABA systems.	76
17	Cinnamon (*Cinnamomum verum*)	Cinnamaldehyde, Eugenol	Inhibition of NF-κB activation and nitric oxide synthesis; reduction of serum high-sensitivity C-reactive protein (hs-CRP) and systemic oxidative stress.	77
18	Citron (*Citrus medica*)	Limonene, Hesperidin	Antioxidant and anti-inflammatory activity; inhibition of PGE2 generation and dampening of trigeminovascular head pain signaling.	78
19	Kudzu (*Pueraria lobata*)	Puerarin, Daidzin	Modulation of 5-HT2A serotonin receptors; regulation of cerebral blood flow and inhibition of neurogenic dural vasodilation.	79
20	Rosemary (*Rosmarinus officinalis*)	Rosmarinic acid, Carnosic acid	Inhibition of complement pathway activation; suppression of lipid peroxidation; modulation of central cholinergic and GABAergic tone.	80
21	Lemon Balm (*Melissa officinalis*)	Rosmarinic acid, Citral	Inhibition of GABA-transaminase (GABA-T) resulting in increased brain GABA concentration; cholinergic modulation relieving stress-triggered vascular headaches.	81
22	Black Pepper (*Piper nigrum*)	Piperine	TRPV1 receptor desensitization; enhancement of intestinal absorption/bioavailability of co-administered polyphenols; suppression of IL-1β and TNF-α.	82
23	Ashwagandha (*Withania somnifera*)	Withanolides (Withaferin A)	Modulation of the HPA axis and cortisol levels; GABA-mimetic activity in the CNS; attenuation of neuroinflammation and neurovascular oxidative stress.	83
24	Chinese Skullcap (*Scutellaria baicalensis*)	Baicalin, Baicalein, Wogonin	Selective 5-LOX and COX-2 enzyme inhibition; suppression of microglial neuroinflammatory activation and blood-brain barrier disruption.	84
25	Garlic (*Allium sativum*)	Allicin, S-allylcysteine	Inhibition of platelet aggregation; elevation of hydrogen sulfide (H_2S) and regulation of endothelial nitric oxide synthase (eNOS) tone.	85
26	Passionflower (*Passiflora incarnata*)	Chrysin, Vitexin	Binding to GABA-A receptor benzodiazepine binding sites; central anxiolytic and muscle-relaxing effects preventing stress-triggered attacks.	86
27	Black Seed (*Nigella sativa*)	Thymoquinone	Scavenging of superoxide free radicals; inhibition of COX and 5-LOX inflammatory eicosanoids; attenuation of trigeminal sensory afferent firing.	87
28	Bushy Matgrass (*Lippia alba*)	Citral, Carvone, Myrcene	Antinociceptive effects mediated via central adenosine A_2A receptors and endogenous opioid system interaction; vascular smooth muscle relaxation.	88

29	Saffron (*Crocus sativus*)	Crocin, Safranal, Crocetin	Inhibition of monoamine (serotonin, dopamine, norepinephrine) reuptake; neuroprotective and antioxidant activity within trigeminal ganglion neurons.	89
30	Licorice (*Glycyrrhiza glabra*)	Glycyrrhizin, Liquiritigenin	Glucocorticoid-like anti-inflammatory action; suppression of HMGB1-mediated neuroinflammation and inhibition of 11-beta-HSD enzyme.	90
31	Green Tea (*Camellia sinensis*)	EGCG, L-theanine	EGCG inhibits NF-κB and STAT3 neuroinflammatory signaling; L-theanine antagonizes glutamate receptors and promotes alpha-wave relaxation, dampening cortical excitability.	91

METHODS:

Pre-formulation and Processing of Active Ingredient

Extraction and Standardization

The target bioactive phytoconstituents are isolated using supercritical carbon dioxide (sCO_2) extraction or solvent extraction with ethanol, followed by concentrated rotary evaporation and freeze-drying [55]. The resulting extract is quantified and standardized using High-Performance Liquid Chromatography (HPLC) against authenticated reference standards [55,56].

Particle Size Reduction (For Suspension pMDIs)

For suspension-based pMDIs, the dried standardized extract is micronized using a Fluid Energy Jet Mill operated with dry nitrogen gas at an injection pressure of 5–6 bar [92]. Particle size distribution (PSD) is verified via laser diffraction (Malvern Mastersizer) equipped with a dry powder module, maintaining d_{90} < 5.0 µm to ensure targeted pulmonary deposition [92-93].

Preparation and Filling of pMDI Formulations

pMDI units are prepared using the **Pressure Filling Method** under controlled environment conditions (20 ± 2° C and 45–55% RH) [58,94]:

1. **Concentrate Preparation:** A measured amount of standardized extract (0.1–1.0% w/w) and surfactant (0.01–0.1% w/w) is dissolved in dehydrated ethanol (5–15% w/w) under continuous magnetic stirring at 300 rpm for 15 minutes [59,94].
2. **Dosing & Valve Crimping:** Aliquots of the liquid concentrate are dispensed into dry anodized aluminum canisters. A 50 µL metering valve is crimped onto the canister neck using a pneumatic aerosol crimper set to a crimp height of 5.6–5.8 mm [60,94].
3. **Propellant Pressure Filling:** Liquefied HFA-134a or HFA-227ea propellant is pressure-filled through the metering valve stem into the sealed canister via a semi-automated benchtop aerosol filler [57,94].
4. **Homogenization:** Canisters undergo ultrasonic bath treatment for 10 minutes to ensure uniform dispersion or complete solubilization Units are stored upright for 24 hours prior to testing [59].

In Vitro Quality Control and Characterization

1. **Leakage Test and Net Content**

Canisters are weighed (W_1), stored inverted at 25 ± 2° C for 14 days, and re-weighed (W_2) according to United States Pharmacopeia guidelines [95]. The annual leakage rate (mg/year) is calculated as:

Leakage Rate = (W_1- W_2) /Time X 365

Units exhibiting a leakage rate >0.5% per year of total fill weight are discarded [95].

2. **Delivered Dose Uniformity (DDU)**

Delivered dose uniformity across the canister life (beginning, middle, and end actuations) is determined using a Dose Uniformity Sampling Apparatus (DUSA) connected to a vacuum pump calibrated to 28.3 L/min [95,96]. Actuations are discharged into the DUSA tube fitted with a 47 mm quartz fiber filter, washed with methanol, and quantified by validated HPLC [95].

3. Spray Pattern and Plume Geometry

Spray pattern cross-sectional area, ellipticity, and plume angle are characterized using a non-articulating high-speed laser imaging system under controlled actuation forces [97]. Measurements are taken at 3.0 cm and 6.0 cm distances from the actuator orifice during the fully developed actuation phase (10–30 ms) [97].

4. Particle Morphology

For suspension formulations, particle morphology and physical state after propellant evaporation are analyzed using Scanning Electron Microscopy (SEM) operated at an accelerating voltage of 5.0–10.0 kV after gold sputter coating under vacuum [98].

CONCLUSION

The transition from conventional oral triptans to advanced pulmonary delivery systems represents a promising frontier in acute migraine therapy. While standard oral formulations suffer from delayed clinical onset, reduced bioavailability, and gastrointestinal impairment during acute attacks, pressurized metered-dose inhalers (pMDIs) capitalize on the extensive alveolar surface area and thin epithelial membrane to achieve rapid, non-invasive systemic drug delivery while bypassing hepatic first-pass metabolism. Incorporating standardized botanical bioactives—such as those from *Tanacetum parthenium*, *Petasites hybridus*, *Zingiber officinale*, *Mentha piperita*, and *Cannabis spp.*—into aerosolized formulations offers a multi-targeted therapeutic approach. These phytoconstituents directly modulate key pathophysiological cascades of migraine, including trigeminovascular neuroinflammation, CGRP release, 5-HT receptor signaling, and cortical spreading depression. Transforming these botanical active ingredients into viable clinical therapies requires meticulous pharmaceutical engineering and rigorous quality control. Achieving target particle sizes ($d_{90} < 5.0$ µm) through jet-mill micronization, optimizing propellant-cosolvent matrices, and verifying performance via Next Generation Impactor (NGI) and Delivered Dose Uniformity (DDU) testing are critical to ensuring reliable deep-lung deposition. Although historical usage and preclinical evidence are compelling, well-designed clinical trials and standardized phytochemical profiling remain essential to establish safety, efficacy, and regulatory compliance. Ultimately, scientifically validated herbal pMDIs offer a promising, fast-acting, and non-invasive paradigm for rapid migraine relief.

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