



Review On Jellies For Motion Sickness

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Abstract:

Motion sickness is a common and complex syndrome that occurs in response to either real or perceived motion. Its presentation can be diverse and may include gastrointestinal, central nervous system, and autonomic symptoms. The main symptom of motion sickness is typically nausea. Plant play a vital role in curing various ailments of the man and herbal remedies are getting increasing patient compliance as they are devoid of typical side effects of allopathic medicines. So there is need to investigate such drugs and their effective formulation for the better patient acceptance. While considering paediatric population the main problem is at what age children can safely swallow an oral medication especially tablets and capsules. Jellies can be easily swallowed even by children who does not have their primary teeth. For any paediatric formulation taste, colour, flavour, texture and its acceptance are very important. Considering these facts present review aims to develop novel herbal jellies containing the herbs, *zingiber officinalis*. The rhizomes of *Zingiber officinale* (ginger) have been used since ancient times as a traditional remedy for gastrointestinal complaints. The most active ingredients in ginger are the pungent principles, particularly gingerols and shogaols. This review focus on the current status of the therapeutic potential and phytochemical profile on the herbal *zingiberofficinalis*. It can also provides the better information regarding to the formulation and evaluation parameters of the novel herbal Jellies for motion sickness and to provide the better therapeutic effects to patient compliance.

Keywords: Motion sickness, Paediatric, *zingiberofficinalis*, gingerols, shagols, jellies.

Introduction:

During the past decade, the therapeutic use of herbal medicine is gaining considerable momentum in the world.^{1,2} The use of herbal medicine due to toxicity and side effects of allopathic medicines, has led to sudden increase in the number of herbal drug manufactures. Herbal medicines as the major remedy in traditional system of medicine have been used in medical practices since antiquity.^{3,4,5} <https://www.ncbi.nlm.nih.gov/books/NBK539706>

Motion sickness symptoms were first described by Hippocrates, who wrote, “sailing on the sea proves that motion disorders the body.”^{6,7,8} The main symptom of motion sickness, nausea, is derived from *naus*, the Greek word for ship (e.g., nautical).^{9,10} <https://onlinelibrary.wiley.com/doi/10.1111/cns.12468>

Etiology:

Motion sickness is typically triggered by low-frequency lateral and vertical motion (example: air, sea, road transportation) or by virtual simulator motion (video games, virtual simulators). The sensory conflict and neural mismatch theory is the most widely accepted theory for explaining motion sickness.^{11,12} It describes the conflict that occurs between the visual, vestibular and somatosensory systems resulting from real or virtual motion. Afferents from the vestibular apparatus arrive at the vestibular nuclei of the brainstem, which also receives inputs from the visual and proprioceptive systems. Efferent projections then reach the temporoparietal cortex via the posterolateral thalamus, triggering autonomic reactions and the vomiting center^{13,14,15}. When there is a discrepancy between actual versus expected patterns of vestibular, visual, and kinesthetic inputs, it initiates the cascade of motion sickness symptoms. <https://my.clevelandclinic.org/health/articles/12782-motion-sickness>

Epidemiology

Motion sickness is inducible in almost all people with a functioning vestibular apparatus and a sufficient provocative stimulus. Patients with a total loss of labyrinthine function are immune to motion sickness^{16,17,18}. <https://www.ncbi.nlm.nih.gov/books/NBK539706/>

Individual susceptibility varies. Certain characteristics associated with motion sickness include:

- **Sex** – women are more susceptible than men
- **Age** – motion sickness begins around age 6 and peaks at age 9 - there is a subsequent decline during teen years due to habituation
- **Elderly people** are the least susceptible to motion sickness
- **Fitness level** – cross-sectional studies show increased susceptibility in persons with high levels of aerobic fitness; there have been suggestions that this is due to a more reactive autonomic system
- **Medical conditions** – patients with vertigo, vestibular pathology, Meniere's disease, and migraines are at elevated risk
- **Hormones** – fluctuations during pregnancy and the menstrual cycle increase susceptibility.^{19,20}

• **Marketed synthetic drug formulations for motion sickness:**

- **Promethazine hydrochloride (PMZ)** : a first-generation antihistaminic agent which is derived from phenothiazine, inhibits the action of natural histamine by blocking histamine H₁ receptors.^{21,22,23}
- Promethazine is currently available in three oral dosage forms: **syrup, tablet, or elixir**. Usually, 25 mg of promethazine is administered orally every 4 to 6 h when used to treat nausea and vomiting. It is widely used to control dizziness, motion sickness, nausea and vomiting .
- Administration of conventional tablets requires water, particularly in the case of motion sickness and coughing during the common cold, allergic conditions and bronchitis. Hence, it is common for nauseous patients to take promethazine via direct intravenous injection or suppository ^{24,25}

<https://www.sciencedirect.com/science/article/pii/S1319016421000682>

- **Cinnarizine is an H1-receptor antagonist.** It is widely used in the treatment of motion sickness, vomiting. It is water insoluble and tasteless drug. Hence it was selected as a model drug for the preparation of **oral dispersible tablets**. The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing accurate dosage, and most importantly the patient compliance. However, the most evident drawback of the oral dosage forms, such as tablets and capsules, is difficulty in swallowing, leading to patients in compliance particularly in case of pediatric and geriatric patients. The development of solid dosage form that disintegrates rapidly or dissolves even when taken orally without water are being formulated. This dosage form is known as oral dispersible tablets.^{26,27,28}
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6841794/>
- **Dimenhydrinate:** is an over-the-counter medication that is used to relieve nausea, vomiting, and vertigo caused by motion sickness
- Dimenhydrinate (DMH) is an over-the-counter antihistaminic drug that is often used as an antiemetic to prevent and treat nausea, vomiting, dizziness, and vertigo associated with motion sickness. The application of Transdermal Drug Delivery (TDD) technology in the formulation of pharmaceutical products has become increasingly important in the past few decades, as it has many merits
The transdermal patch can deliver drugs steadily over a long period of time, with minimal adverse effects or treatment failure. This drug-administration route can avoid the first-pass metabolism and significantly improve the drug bioavailability and therapeutic outcomes. TDD systems such as patches, gels, and films are non-invasive, painless dosage forms and require a simple application. Therefore, TDD excels compared to other drug-administration methods and has already achieved a high patient compliance. Fortunately, many drugs are candidates for transdermal delivery, such as drugs with a very short half-life, narrow therapeutic window, or poor oral availability.^{27,28,29}
<https://www.sciencedirect.com/topics/neuroscience/dimenhydrinate>
- **Scopolamine hydrobromide (SCOP)** :Is available in market to treat motion sickness SCOP in situ gels at 0.2%, 0.5%, and 1.0% gellan gum concentration (w/v) were prepared, respectively, and characterized in terms of viscosity, in vitro release, and nasal cytotoxicity. Single photon emission computed tomography technique was used to evaluate the nasal residence time of gel containing (99m)Tc tracer. The antimotion sickness efficacy produced by the in situ **gel formulation** was investigated in rats and compared with those achieved after subcutaneous and oral administration.^{31,32,33} <https://pubmed.ncbi.nlm.nih.gov/17376300/>
- **Metoclopramide (MCP):** It can be effectively alleviate motion sickness-caused nausea and vomiting. Nasal administration offers the greatest patient compliance. It is suitable for self-administration and offers rapid and complete absorption, no first-pass effects and high bioavailability. MCP **nasal spray** prepared here is safe with minimal cytotoxicity, rapid onset and high relative bioavailability.^{34,35,36}
- <https://medlineplus.gov/druginfo/meds/a684035.html>
- **Cinnarizine:** is used for the treatment of nausea and vomiting, motion sickness. So in case of motion sickness, vomiting and nausea, it required immediate release of drug from the dosage form, which make Cinnarizine suitable candidate for the **mucoadhesive microsphere**. Cinnarizine, developed as an anti-histamine, subsequently manifested a number of pharmacological effects, most significantly: labyrinthine suppressant action and peripheral antivasoconstrictive effects. Cinnarizine inhibits smooth muscle cell contraction in the vasculature by blocking L-type voltage-gated calcium channel. It is also known to bind to histamine H1 receptors, muscarinic (acetyl choline) receptors and dopamine D2 receptors. Thus, the mechanism of action of cinnarizine is multimodal. Insufficient cerebral blood circulation has been hypothesized to cause 'vertiginous symptoms' like tinnitus, © 2022 JETIR June 2022, Volume 9, Issue 6 www.jetir.org (ISSN-2349-5162) JETIR2206637 Journal of Emerging

Technologies and Innovative Research (JETIR) www.jetir.org g312 dizziness nausea and vomiting in a range of conditions including transient ischemic attacks. Cinnarizine's antivasoconstrictive and protective action against hyperviscosity of blood along with its peripheral anti-ischemic action may be helpful in improving blood flow thus playing an important role in various therapeutic indications.^{37,38,39}

<https://www.jetir.org/papers/JETIR2206637.pdf>

- **Marketed herbal drug formulations for motion sickness:**

Ginger powder: Ginger extract showed peripheral antiemetic activity in dog but it did not act on central nervous system. This anti-emetic effect is caused by synergism between zingerone and shogaol. A clinical study showed that the oral treatment of 90 g powdered ginger was more effective in comparison to dimenhydrinate in reducing motion sickness symptom.^{40,41}

<https://www.intechopen.com/chapters/68980>

Gliadin : Medicated chewing gum (MCG) has gained increasing acceptance as a drug delivery system. In this system, drug is buccally absorbed eventually reaching the systemic circulation

Medicated chewing gum is beneficial than other conventional dosage forms because it offers faster onset of action and an excellent possibility for the delivery of metabolically unstable drugs. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route Gliadin, a storage protein of *Triticum aestivum* (wheat grain) (family Gramineae) called as prolamin, is one example of the natural gum base having good chewiness .Gliadin is extracted from wheat flour grain using 70% aqueous ethanol.

Recently, spray-dried microparticles comprising nicotine bitartrate and hypromellose were formulated for incorporation into medicated chewing gum.⁴³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4674635/>

Ginger Chewing a gum: helps reducing nausea and thus, ginger chewing gum can even control nausea during motion sickness preferably. The main effects of ginger allocate to some phenolics such as gingerols and shogaols that act as their active agents^{44,45,46,47}

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4976530/>

Topical Jellies Formulations:

Oral medicated jellies are the palatable Solid dosage form administered in the oral cavity ,meant to dissolve in mouth or pharynx fir its local or systemic effect. Patients are usually comfortable with oral drug delivery system since it is noninvasive and usually offers low cost of treatment.^{48,49}

“Jelly can be define as transparent or translucent non-greasy, semisolid preparation meant for external as well as internal applications” the medicated jelly has through years gained increasing acceptance as a drug delivery system.^{50,51}

<https://www.jpsr.pharmainfo.in/Documents/Volumes/vol12issue07/jpsr12072009>

TYPES OF JELLIES:

a) Medicated jelly: These are mainly used over mucous membrane and skin and they possess spermicidal, local anaesthetic, and antiseptic properties. These jellies hold adequate amount of water which after evaporation gives a local cooling effect and residual film provides protection.

b) Lubricating jelly: These jellies are intended for lubrication of equipment used in diagnosis like surgical glove, catheters, cytosopes.

c) Miscellaneous jelly: These are meant for various applications like patch testing, electrocardiography.^{51,52}

<https://www.researchgate.net/publication/337394779>

- **Gelling agent:** It should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.

<https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/gelling-agent>

- Be compatible with taste masking .
- Effective taste masking technologies should be adopted for bitter taste drug.
- Be portable without fragility concern.
- Leave negligible or no residue in the mouth after oral administration.
- Allow high drug loading
- The drug and excipients property should not affect the orally disintegrating tablet.^{53,54}

Challenges in formulating oral medicated jelly :

- **Palatability:** Masking taste of bitter drug and enhancing taste directly related to patient compliance.
- **Hygroscopicity:** some oral jelly dosage form are hygroscopic and they need protection from humidity so need specialized product packaging.
- **The drug property:** solubility, crystal morphology, particle size and bulk density of affected the final jelly characteristics.
- **Mouth feel:** medicated jellies leave minimal or no residue in mouth after oral administration.^{55,56}

OBJECTIVES OF ORAL MEDICATED JELLIES : To develop a formulation which is dissolved in mouth of pharynx which is local or systemic effect

1. To increase patient compliances
2. To use poorly soluble drug in medicated jelly
3. Formulation of chipper dosage form then conventional formulation.

Advantages of medicated jellies:

- 1.It can be administered easily i.e. anytime,anywhere as it is easy to handle & doesn't required water.
- 2.Therapeutic action of drug can be terminated by spitting it before complete ingestion of medicated jelly.
- 3.It serve as ideal method of drug delivery for dysphasia patient as reduced the risk of aspiration.
- 4.Good mouth feel property of jellies help to change the perception of medication.
- 5.Rapid onset of action.
- 6.The treatment can, if required,be terminated at any time. ⁵⁷

https://www.researchgate.net/publication/324836079_

Disadvantages of medicated jelly:

- As it is aqueous based preparation it need to appropriate packaging to maintain stability of drug in various environment.
- It may lead to unpleasant taste if not formulated appropriately.

VARIOUS COMPONENTS OF MEDICATED JELLY FORMULATION:

I. Gelling Agent: These are hydrocolloids, which form gel like matrix. It dissolve in liquid phase and form weak cohesive internal structure. Examples of gelling agents:^{58,59}

<https://www.jpsr.pharmainfo.in/Documents/Volumes/vol12issue07/jpsr12072009>.

a) Sodium Alginate: Alginate is obtained from the cell wall of brown algae .Alginates bind with water and forms thick gum. It is used in various oral and topical pharmaceutical formulations. It is generally used as thickening agent and suspending agent in various topical formulations such as pastes, creams and gels.

b) Pectin: It is a heteropolysaccharide obtained from cell walls of terrestrial plants. It is used against constipation & diarrhoea, where it increases viscosity & volume of stool. Due to its lesser cost it is used in various delivery methods like controlled release, mucoadhesive, gastroretentive, colon- specific drug delivery systems. Also used as stabilizer in cosmetics.

c) Tragacanth: Tragacanth gum works as an emulsifying and suspending agent in various pharmaceutical preparations such as emulsion, gels, and creams. Also used as thickener, stabilizer, & texturant additive in foods & pharmaceutical

d) Gelatin: Gelatin is generally used as gelling agent in pharmaceutical preparation, vitamin capsules, cosmetic technology, & photographic emulsions. Also used in implantable delivery system to deliver drug suspended in biodegradable matrix.

e) Xanthan Gum: It is commonly used as a thickening, emulsifying, suspending and stabilizing agents in oral, topical pharmaceutical formulations, cosmetic, and food products. Used as binder in tooth paste & keeps the product uniform. Used as a hydrocolloid in the food preparations & thickening agent in shampoos.

f) Cellulose derivatives: Used as emulsifier & thickener in food & cosmetic preparations. Also used for relief from constipation problem E.g. Methyl cellulose, Sodium carboxy methyl cellulose.

g) Agar: Agar-agar is vegetarian product & substitute to gelatine. It is obtained from algae & is white and semitranslucent. It has various applications such as thickener, gelling agent, texturizer, moisturizer, emulsifier, flavour enhancer, and absorbent in pharmaceuticals & food products.

h) Carrageenans: It is obtained from extracts of red edible seaweeds, & are linear sulfated polysaccharides. They are mainly used as gelling, thickening, and stabilizing agents in food & pharma industry. Carrageenan is vegetarian & is used as substitute for gelatine in confectionery

II. Sweetners:

a) Sucrose: Sucrose was most preferred sweetening agent because it is soluble in water, it is economical i.e., its highest purified form can be obtained at reasonable price, physically and chemically stable in different pH. It is widely used in combination with sorbitol, glycerin and other polyols to prevent crystallization of sucrose.^{60,61,62}

b) Dextrose: They are anhydrous & monohydrate form of dextrose, among them anhydrous form is hygroscopic in nature.

c) Mannitol: Mannitol is a white, crystalline polyol obtained by hydrogenation of fructose. It imparts a mild cooling sensation when it is chewed or dissolved in the mouth due to its negative heat of solution.

d) Saccharin: It is an artificial sweetening agent. It is about 250-500 times sweet as sucrose. It has excellent stability, saccharin sodium & calcium has excellent water solubility.

e) Sucralose: It is an artificial sweetener. It is thermostable and also remains stable in wide pH range. Hence it can be used in products that need a longer shelf life. Compared to sucrose onset of sweetness occurs slowly but sweetness remain for longer duration of time.

f) Sorbitol: Sorbitol is a sugar alcohol & isomer of mannitol. It is about 60% as sweet as sucrose. It is obtained from corn syrup or by reduction of glucose. It is used as humectant & thickener in cosmetics, used as laxative, formulation of soft gel capsules & in treatment of hyperkalaemia.^{63,64}

III. Colouring agents: Colourants are used for the following reasons:

- a) To provide aesthetic appearance to dosage forms
- b) To increase patient acceptance
- c) To maintain colour uniformity of the dosage form.
- d) Help in product recognition and differentiation.

Types of Colouring agents: a) Natural Colours It is extracted from natural sources or chemically synthesized such as beta-carotene.

b) Mineral Colours Example of Mineral colour include mixture of red & yellow ferric oxides gives flesh colour to calamine lotion

c) Dyes These are synthetic chemical compounds that imparts colour when it is dissolved in a solvent such as propylene glycol and glycerine. It contains 80 to 93% pure colorant material.

d) Lakes Lakes are aluminium salts of FD&C water soluble dyes extended on a substratum of alumina. Lakes prepared from calcium salts of FD&C dyes are also permitted.^{65,66}

IV. Flavouring Agents : Taste Flavours used

Acidic: Orange, lemon, cherry,

Alkaline: Vanilla, chocolate, mint

Bitter :Orange, anise, lemon Metallic Grape, berry

Sweet: Honey, chocolate, raspberry,

V. Preservatives: Jellies are prone to microbial attack. Preservation is must in order to avoid at all any incompatibilities between gelling agents & to retain the shelf life of product.

Eg: Methyl Paraben, Propyl Paraben, Benzoic Acid, Benzalkonium Chloride, Chlorhexidine acetate.

VI .Stabilizers:Stabilizers are used to maintain desirable properties of product .It is used to prevent the drying of jellies. Examples: Propylene glycol and Sorbitol. Chelating Agents are used to avoid any reactivity between base or medicament with heavy metals e.g. EDTA.^{67,68,69}

- **Evaluation of Medicated Jelly:**

<https://ijpsr.com/bft-article/formulation-and-evaluation-of-medicated-oral-jelly-of-trazadone-hydrochloride/>

•**Physical appearance:** The medicated jelly was examined for physical appearance in terms of clarity, texture and consistency.^{70,71}

•**Stickiness and grittiness:**Texture of the medicated jelly in terms of stickiness and grittiness had been evaluated by visual inspection of the product after mildly rubbing the jelly sample between two fingers.

•**Spreadability:**For the determination of spread ability sample of jelly was applied between two glass slide compressed to uniform thickness by placing 1000gm weight. The time required to separate the two slide moves over the slide was taken measured of spread ability. $S = m * L / T$ Where m= weight tide to slide L= length moved on glass slide T= time taken

•**Viscosity:**Viscosity had been measured using brookfield viscometer. As the system nonNewtonian spindle no.4 was used.^{72,73,74}

•**pH:**The pH of all the jelly was determined using digital pH meter. 0.5gm of the weight formulation was dispersed in 50ml of distilled water and pH was noted.

• **Drug content:** The jellies are selected and crushed in a mortar and then mixture equivalent to that of drug was and dissolved in 100ml of volumetric flask containing 6.8pH buffer and final volume was made up to the mark. Then the solution was filtered and diluted appropriately, and analysed spectrophotometrically using uv spectrophotometer.^{75,76,77}

•**Stability studies:**The jellies formulation were packed in aluminium foil and stored in polyethylene containers at 0°C, 25°C/60% RH for 90 days.^{78,79,80}

CONCLUSION:

Motion sickness is very common syndrome. It is an unpleasant condition that occurs when persons are subjected to motion or the perception of motion.^{81,82,83} Jellies are rarely available for its treatment. Pharmaceuticals jellies have aesthetic appearance and pleasant taste than any other oral drug delivery systems. It has better organoleptic properties and patient compliance. Paediatrics and dysphagia patients can utilize the formulation more effectively and easily.^{84,85} By controlling the viscosity of jelling agent, rate of drug release and drug plasma level can be controlled.

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