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FAST DISSOLVING ORAL FILM: A BOON FOR PATIENTS SUFFERING WITH NAUSEA AND VOMITING

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ABSTRACT
For patients receiving chemotherapy and radiation therapy, nausea and vomiting are serious issues. Moreover, post-operative nausea and vomiting are common side effects. Postoperative nausea and vomiting (PONV) is thought to occur in 25–30% of cases. Furthermore, oral thin films provide accurate and adaptable dosing. Oral films are made easier and more convenient by these qualities, which also have positive medicinal effects. Drugs are rapidly absorbed in the mouth when administered via buccal or sublingual film delivery. This reduces exposure to the gastrointestinal system and addresses issues that are frequently related to tablets and capsules, including first-pass metabolism, gastrointestinal adverse effects, and sluggish or restricted absorption in the GI tract. Consequently, buccal or sublingual films might provide increased patient compliance, decreased adverse effects, and higher absorption. This article provides a thorough understanding of emesis, including its causes, treatments for emesis, innovative oral thin-film drug delivery, its properties, methods for fabrication and assessment, and, finally, previously published research on antiemetic oral thin-film.

Keywords: vomiting, emesis, oral thin film, the degree of bioavailability innovative method of medication administration.

INTRODUCTION

The strong retrograde ejection of stomach contents from the body is known as vomiting, or emesis. The uncomfortable feeling that comes before vomiting is called nausea. Vomiting is often the cause of relief from nausea and can be followed with pallor, bradycardia, salivation, diaphoresis, and a decrease in breathing rate, which are all signs of enhanced parasympathetic nervous system activity. The simultaneous contraction of the muscles of inspiration and the abdominal cavity that can happen when vomiting is known as "dry heaves" or retching [1].

It is important to distinguish between vomiting and eructation (belching), which is the release of stomach air that has been swallowed, as well as regurgitation, which is the gentle passage of stomach contents

into the esophagus. Eructation or regurgitation may be the result of the lower esophageal sphincter malfunctioning or it may be voluntary. Although diverticula, mucosal rings, cancer, and diseases of esophageal motility, like achalasia and diffuse spasm, might mimic the appearance of vomiting, the food bolus never reaches the stomach [2].

Neural and humoral mechanisms can both cause vomiting. There are six basic components that make up the neural pathway. The CRTZ, the higher regions of the brain, the vestibular apparatus, and the gastrointestinal tract (afferent neurons) all provide information to the emetic center. Lastly, the vomiting center uses the efferent motor neurons to provide signals that coordinate the vomiting reflex. The gastrointestinal tract, in particular the duodenum, as well as other regions such the liver, pancreas, peritoneum, heart arteries, and reproductive and urinary systems, are the source of the vagal and sympathetic afferent neurons. These neurons' stimulation starts the impulse that goes straight to the emetic center [3]. Three mechanisms can cause emesis in the higher brain centers, such as the limbic system and the cerebral cortex: direct stimulation of the vomiting center by neoplasia, hydrocephalus, or inflammatory diseases; psychogenic stimulation brought on by fear, stress, excitement, or pain; and traumatic stimulation brought on by head injuries and elevated intracranial pressure [4].

Drug categories used to treat emesis

- **Steroids:** To better prevent nausea and vomiting, they are frequently administered in combination with other anti-emetic medications. They may be administered both before and after therapy. Steroids are sometimes not used for nausea and vomiting due to potential adverse effects that could exacerbate a patient's existing medical conditions. (For instance, dexamethasone) [5].
- **Dopamine antagonists:** To aid in preventing dopamine from attaching to brain regions that cause nausea and vomiting, they target this chemical. These medications are often administered when other medications are not effective in controlling nausea and vomiting. (For instance, metoclopramide and prochlorperazine.) [6].
- **Benzodiazepines:** By lowering anxiety and promoting calmness and relaxation, they can lessen nausea and vomiting. These medications are frequently used in conjunction with other anti-nausea medications and may be more beneficial for people who experience anticipatory nausea and vomiting. (For instance, lorazepam and alprazolam) [7].
- **Serotonin (5-HT3)**: These antagonists prevent serotonin from having its usual impact of causing nausea and vomiting. These medications, which are typically administered prior to chemotherapy and for a few days following the treatment, are useful in managing acute nausea and vomiting. (For instance, granisetron, dolasetron, palonosetron, and ondansetron.) [8].

- **Cannabinoids**: They have the psychoactive component of marijuana in them. When the standard anti-emetic medications fail to relieve chemotherapy-induced nausea and vomiting, these medications may be utilized. They can also be used to increase hunger (Nabilone, dronabinol, for example) [9].
- **NK-1 receptor antagonists:** They prevent the effects of the NK-1 receptor, which is involved in the reflexive vomiting response. These medications are sometimes used to treat acute nausea and vomiting in addition to their assistance with delayed nausea and vomiting. They frequently accompany other anti-nausea medications. (For instance, rolapitant, fosaprepitant, and aprepitant.) [10].

Different ways in which anti emetic drugs are administrated

- Using an intravenous (IV) drip;
- Orally as a pill or liquid that you ingest;
- As a tablet that dissolves beneath your tongue;
- As a suppository;
- Or via a skin-sticking patch [11].

Novel drug delivery system

Because of its simplicity, adaptability, non-invasiveness, patient compliance, and acceptability, the oral route is the most recommended method of drug administration for systemic impact [12]. Because tablets are easier to manufacture, transport, and increase patient compliance, they are the most popular dosage form. Patients who are elderly, young, queasy, bedridden, and noncompliant typically have trouble swallowing the traditional oral dosage form and don't take their medications as directed.

Fast dissolving drug delivery systems, often referred to as fast dissolving/disintegrating film, are a new generation of drug delivery systems that were developed in the late 1970s as an alternative to tablets, capsules, syrups, and other formulations for oral drug delivery [13].

Based on the transdermal patch technique for oral medication delivery, a fast-dissolving oral film was created. The medicine is delivered via a thin, postage-stamp-sized film that is applied to the patient's tongue or mucosal tissue. The film absorbs saliva and promptly hydrates the area, releasing the drug for absorption by the oral mucosa. The main cause of this swift dissolving action is the film's enormous surface area, which wets rapidly when exposed to the moist oral environment [14].

Fast Dissolving Oral Films

The oral route is the one that patients find most agreeable out of all the options. The majority of pharmaceutical companies have focused their research efforts on creating workable oral dosage alternatives for patients who are nauseated, noncompliant, elderly, or in pediatrics. Oral medication delivery research has resulted in the development of a variety of dosage forms, including wafers, modified release tablets, conventional tablets, and oral disintegrating tablets. More recently, fast-dissolving oral films have been developed [15].

Flat sheets called oral thin films are inserted into the mouth. They are designed to dissolve in the oral cavity in a matter of seconds and are made of incredibly thin polymeric strips with an active medicinal component. This dosage form is helpful since the medication acts quickly through the oral mucosa [16]. They are referred to as "orodisperse" tablets in the European Pharmacopoeia, and are meant to be taken inside the mouth where they quickly scatter before swallowing. Fast dissolving films are a globally recognized and tested method for the systemic drug delivery of active pharmaceutical ingredients (API) [17].

Fast dissolving films are a kind of oral medication delivery method that was created using transdermal patch technology for oral drug delivery. With this delivery method, a thin film is applied to the patient's tongue or mucosal tissue and quickly moistened by saliva. It then quickly dissolves and disintegrates, releasing the drug for absorption through the oral mucosa [18].

Hydrophilic polymers are used to make fast-dissolving oral films, which disintegrate quickly on the tongue or in the buccal cavity and release the medication into the bloodstream upon contact with liquid. An improved substitute for the conventional pills, capsules, and liquids frequently found in prescription and over-the-counter drugs is fast-disposing oral film. Thin-film strips, which resemble a postage stamp in size, shape, and thickness, are usually used for oral administration. The user places the strip on the inside of the cheek (buccal) or beneath the tongue (sublingual). By avoiding the first pass metabolism, these drug delivery methods increase the medication's bioavailability. The medication may enter the bloodstream sublingually, enterically, or buccally as the oral thin film dissolves [19].

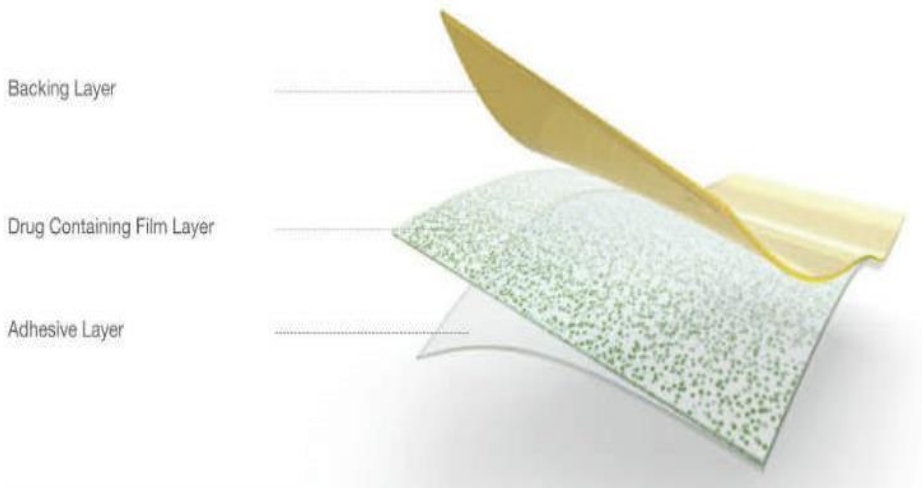

Figure 1: Oral thin films

Types of film

1) Film with flash release
2) Dispersible flash film
3) Mucoadhesive films that do not disintegrate
4) Mucoadhesive films that disintegrate moderately

Advantages

- The following are some unique benefits that oral films have over other oral dose forms:
- Due to its wide surface area, which reduces dosage intervals and enhances therapy's onset of action, efficacy, and safety profile, it dissolves and disintegrates quickly in the oral cavity.
- Easy to handle, store, and transport;
- More flexible, compliant, and less brittle than ODTS are the advantages of oral films.
- Every strip or film ensures accuracy in the dose provided.
- Oral films offer new business opportunities from a commercial standpoint, such as product differentiation and promotion [20].

Disadvantages

This delivery system's primary drawback is that huge doses cannot be added to strips or films. Although each Gas-x thin strip from Novartis Consumer Health contains 62.5 mg of simethicone, there are still a number of restrictions associated with using film strips [21].

Method of Preparation of Mouth Dissolving Film

1. Solvent Casting Method: Solvent casting is now the most popular production method for creating oral thin films. This approach involves dissolving the plasticizer and water-soluble polymer in distilled water. To release all trapped air bubbles, the solution is agitated for two hours using a magnetic stirrer

and then left aside. Excipients and API are dissolved in the meantime, and both solutions are well agitated for 30 minutes before being combined. At last, the solution is poured onto a level surface that can be used to form a film. After drying, the film is carefully removed. The creation of an abuse deterrent and microemulsion-based sublingual film of buprenorphine hydrochloride for breakthrough pain treatment was accomplished using the same solvent casting approach [22].

2. Hot melt extrusion: Initially, a solid mixture of medicine and carrier is combined in the hot melt extrusion process. After that, the mixture is melted using an extruder with heaters. Finally, the dies form the melt into films [23].

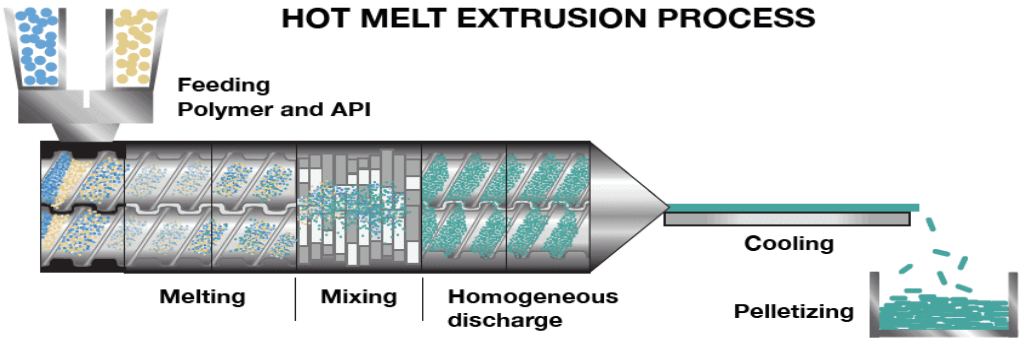

Figure 2: Hot melt extrusion method

3. Semi-solid casting: To create a homogenous viscous solution, a solution of an acid-insoluble polymer (such as cellulose acetate butyrate and phthalate) is combined with a solution of a water-soluble film-forming polymer. It is coated on untreated casting film following sonication. The film should be between 0.015 and 0.05 inches thick after drying. Utilizing the acid-insoluble polymer in a 1:4 ratio with the film-forming polymer is recommended [24].

4. Rolling method: This technique involves rolling a drug-containing solution or suspension on a carrier. The primary solvents are alcohol and water mixtures. After drying on the rollers, the film is cut into the appropriate sizes and shapes [25].

5. Solid dispersion extrusion: Initially, a solid dispersion is created by using a drug to extrude immiscible components, which is then formed into films using dies [26].

Evaluation tests

Morphology study: Scanning Electron Microscopy (SEM) is used to examine the films' morphology at a specific magnification [27].

Organoleptic evaluation: To do this, taste sensors and carefully made equipment are employed in vitro techniques. These in vitro taste evaluation devices are suitable for high-throughput oral pharmaceutical formulation taste screening [28].

Thickness: At various sites, it can be measured with a micrometer screw gauge. Determining the uniformity of the film's thickness is essential since it has a direct bearing on the strip's dosage accuracy.

Folding endurance: The folding durability of the prepared films was measured with great attention. A film strip was repeatedly chopped and folded until it broke [29]. The number of times the film could be folded in the same spot without breaking was used to calculate the value of folding endurance [30].

Weight Variation: The formulations were divided into 4 cm2 films by different batches, and the weights were noted on an electronic balance. For every formulation, three random videos were selected [31]. Ten films from each batch were separately weighed on a digital electronic balance for the weight variation test, and the average weight was calculated [32].

Tensile strength: Tensile strength is the maximum stress applied at the point where the strip specimen fractures. The following equation illustrates how it is calculated: dividing the applied load at rupture by the cross-sectional area of the strip [33].

Tensile strength = Load at breakage / Strip thickness× Strip width

Percentage moisture loss: To confirm the integrity and physical stability of the film, a moisture loss test was conducted [34]. A two-by-two centimeter film was cut and weighed. Following that, the film was kept for three days in a desiccator filled with fused anhydrous calcium chloride. The film patch was taken off and weighed again after three days. The following formula was used to determine the film's percentage moisture loss [35].

Percentage Moisture Loss = (Initial Weight - final weight)/Initial Weight × 100

Drug content: Using a UV spectrophotometer, ascertain the formulation's percentage drug content from the calibration curve [36].

Viscosity: Utilizing a Brookfield viscometer, determine the optimized formulation's viscosity [37].

Disintegration test: Fast dissolving oral strips can be used in accordance with the CDER guidance's 30 second or less disintegration time criteria for orally disintegrating tablets. While there isn't a specific suggestion for oral rapid dissolving films or strips, Jain and Mundada (2015)[38] suggest using this as a qualitative guideline for quality control testing or in the development phase. Ten milliliters of pH 6.8 phosphate buffer were added to a petri plate, and the film was then layered on top. Every ten seconds, shake the Petri plate [39]. The amount of time it took for the film to break down was noted [40].

Stability studies: In accordance with ICH guidelines, oral film samples must be kept for three months at 40±0.5°C and 75±5% RH in order to conduct stability tests. The samples were removed at 0, 30, 60, 90, and 180 days to be checked for drug content [41].

Applications

1. Systems for film formation in the surgical field.
2. It can also serve as a substrate for different kinds of industrial barrier membranes.
3. The use of film-forming polymers improves soil temperature and integrity, both of which are beneficial for crop yield.
4. Non-medical applications of film formners include the delivery of active compounds found in cosmetic items, such as silicone film forming technologies used to make ointments and creams.
5. To treat wounds, film-forming technologies were employed.

Table 1: Fast dissolving oral films of an antiemetic drugs

Name of drug	Excipients used	Method of preparation	Reference
Meclizine Hydrochloride	Xanthan gum, Gelatin, Gum acacia and Methyl Paraben	Solvent casting method	[42]
Metoclopramide	HydroxyPropyl Methyl Cellulose (HPMC) and Poly Vinyl Pyrrolidone (PVP), Glycerol ,Citric acid Meclodin tablet.	Solvent-casting method	[43]
Palonosetron Hydrochloride	HPMC, propylene glycol, maltodextrin	Solvent casting method	[44]
Sumatriptan succinate, Metoclopramide	Hydroxypropyl methylcellulose, propylene glycol	Solvent casting technique	[45]
Metoclopramide Hydrochloride	Hydroxypropyl methyl cellulose, carboxy methyl cellulose	Solvent casting technique	[46]
Prochlorperazine maleate	HPMC E15, Sodium Starch Glycolate IP, Glycerol, Potassium dihydrogen phosphate, Monobasic sodium phosphate, Dibasic sodium phosphate	Solvent casting method	[47]

Domperidone	HPMC E15, PEG-400	Solvent casting method	[48]
Aprepitant	Pullulan and PEG 400 polyethylene glycol	Solvent casting method	[49]
Dextromethorphan Hydrobromide	Hydroxylpropyl methylcellulose E15 (HPMC)	Solvent casting technique	[50]
Rupatadinefumarate	Pullulan and HPMC	Solvent casting method	[51]
Diazepam	Pullulan and Hydroxy propyl methyl cellulose E3, E5, E15 and Hydroxyl propyl β-cyclodextrin and Glycerin, propylene glycol, PEG 400	Solvent casting method	[52]
Granisetron hydrochloride	Polyvinylpyrrolidone/Polyvinyl alcohol	Solvent casting method	[53]
Prochlorperazine	PMC (15 and 47 cps), ethyl cellulose, and PVP	Solvent casting method	[54]
Dimenhydrinate	Hydroxypropylmethyl cellulose E5 (HPMC E5), polyethylene glycol 400 (PEG 400)	Solvent casting method	[55]
Chlorpheniramine maleate	HPMC E3, HPMCE6, HPMCE15, PEG 400, methonal, Citric Acid, Aspartame	Solvent casting method	[56]

CONCLUSION

The most accurate and widely accepted oral dosage form that circumvents the hepatic system and exhibits a greater therapeutic response is the fast-dissolving oral film. Pharmaceutical firms like this dose form since it is both industrially acceptable and has high patient compliance, particularly in the case of

pediatric and geriatric patients. Oral films are a useful tool for product life cycle management; they can take the position of over-the-counter (OTC) medications, both generic and name brand. This technique extends the patent life of current items and is a useful tool for product life cycle management.

Oral medication delivery systems have adopted a revolutionary method with fast dissolving films. A lot of research is being done in this area on a variety of medication categories, and oral fast-dissolving films have become a revolutionary trend. This formulation solves the issue that other sound formulations have. Patient adherence to this formulation is higher in the pediatric and geriatric populations. It is useful in the majority of severe cases because, if placed in the mouth, it will dissolve and enter the bloodstream in a matter of minutes. Thus, it can be said that oral films provide bright future prospects due to their various benefits and good patient compliance.

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