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ORO- DISPERSIBLE FILM: A SOLUTION TO NAUSEA AND VOMITING IN PREGNANCY (NVP)

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ABSTRACT

Common gastrointestinal problems like nausea and vomiting can be brought on by a variety of emetic stimuli via the central and/or peripheral neural systems. When hazardous chemicals, medications, bacteria, viruses, or fungus enter the body through either the GI tract or injectable pathways, such as the cutaneous, pulmonary, or circulatory systems. Most typical pregnancy problem is indigestion and vomiting during gestation. The majority of the time, the symptoms appear in the first phase, but in a minimal number of instances, they can last the entire pregnancy as well as influence the woman's quality of life. Although the etiology of NVP is still not completely comprehended, it's also agreed that the disorder is complex and that a number of hereditary, endocrine, and viral variables may be at play. NVP treatment is currently aimed at reducing hazards to mother and fetus while focusing on alleviating symptoms. The most cutting-edge oral solid dose form is a film that dissolves in the mouth, thanks to its adaptability and user-friendliness. Oro-dispersible films are oral solid medication methods that, if inserted into the mouth without any water or chewing, instantly break down and dissolve. Such a dosage enables the medicament to skip the initial metabolic process, potentially increasing the bioavailability of the drug. This review presents insights on various commercially available mouth dissolving film products, formulation methodologies, and evaluation criteria.

Keywords: Nausea; Vomiting; Pregnancy; Hyperemesis Gravidarum; oro- Dispersible film; Solvent casting

INTRODUCTION:

Both humans and animals with the ability to vomit, these vital defensive mechanisms dodge whether it be ingesting or digesting feasibly hazardous compounds. Emesis is a physical occurrence that involves the violent evacuation of gastric and intestinal contents via the mouth, the uncomfortable urge to vomit that is known as nausea **[1]**. Between 50 and 90 percent of pregnant women often feel vomiting and nauseous (NVP). These symptoms often begin in pregnant women between six and twelve weeks of conception, while some women persist to experience them up until 20 weeks of gestation. At nine-week gestation, the issue is at its worst. A very tiny percentage of these patients develop Hyperemesis Gravidarum, a disease in which the symptoms are severe and necessitate hospital admission due to dehydration, weight loss, and excessive vomiting **[2]**. Vitamin B6 pills have been used traditionally for years to relieve morning sickness **[3]**. Fast-dissolving oral dispersible films are helpful for those patients who could trouble taking conventional pills, such as children, the elderly, and bedridden patients. Consequently, a fast-dissolving oro-dispersible film provides a distinct solid oral dosage type that has important benefits like- they instantly release the active medicinal ingredient by dissolving in the saliva present in the oral cavity **[4-6]**.

Pathophysiology of nausea and vomiting:

It's hypothesized that each person has a fluctuating threshold for nausea. The threshold fluctuates depending on how a person's intrinsic traits interact with their more volatile psychological conditions of fear, thrill, and hope and adaptability at any particular time **[7]**. Inputs from the chemoreceptor trigger zone, the viscera, and the vestibular system are the sources of the stimuli that cause nausea and vomiting **[8]**.

Pathogenesis of NVP:

Despite the fact that the causes of HG and NVP are still unidentified, it's generally agreed to a number of genetic, endocrine, and gastrointestinal variables may play a role:

Genetic predisposition

It seems that a risk factor for NVP is maternal genetics. An additional risk element for HG is a history of the family of the disease; about 28% of women say

that their mothers had the disease in the past, and about 19% report that their sisters experienced signs of the disease. According to these results, if a woman's mother had suffered hyperemesis during pregnancy, her likelihood of developing HG during pregnancy increases by threefold **[9-10]**.

Mechanisms with placental mediation

There has been evidence of the placenta's potential role in the pathophysiology of NVP. It's conceivable that variations in the placenta's features like hormones produced by this organ; prostaglandin E2 produced by the placenta is stimulated by this hormone and reaches its peak between 9 and 12 weeks of gestation **[11]**.

Reproductive hormones

Pregnancy causes a significant change in hormone levels, particularly during the first trimester. According to a number of studies, the signs and symptoms of NVP may be caused both directly and indirectly by the reproductive hormones (hCG, oestrogen, and progesterone) **[12]**.

Progesterone and estrogen

Additionally, progesterone and estrogen, which significantly rise during pregnancy, have been linked to the etiology of HG and NVP. For instance, a high maternal BMI and poor parity, have been connected to an increase in the prevalence of HG. One theory is that NVP might also be influenced by progesterone and estrogen together by changing stomach emptying and perhaps altering smooth muscle contractility **[12-13]**.

Human chorionic gonadotropin (hCG)

hCG hormone has been most frequently linked to NVP and HG pathophysiology. This is primarily supported by the chronological correlation between the highest levels of NVP and hCG, which both correspond to the NVP symptoms that are the most severe, which occur around 9 - 12 weeks of pregnancy **[14]**.

Thyroid hormones

The thyroid gland experiences significant but reversible changes during pregnancy; in fact, the thyroid is overstimulated, which causes it to grow in size. The temporary hyperthyroidism seen in HG patients is what causes hyperthyroidism during pregnancy the most frequently. In actuality, up to 70% of HG-affected women have abnormal thyroid function values. Because TSH is normally repressed because by interacting with the thyroid stimulating hormone (TSH) receptor's alpha subunit, hCG stimulates the thyroid gland **[15-16]**.

Treatment:

While reducing hazards to the mother and fetus, the treatment's objective is to improve symptoms. A multimodal strategy tailored to each person is typically required to achieve this. Treatment options may differ from straightforward diet modifications to medication therapy and complete parental nourishment **[17]**.

I. Non- pharmacological therapy-

1. Emotional Support- Women who have severe symptoms, those whose personality qualities or interpersonal or family issues may be contributing factors, or those for whom behavioral treatment, hypnotherapy, or both, may be helpful. Psychotherapy's fundamental purpose is to motivate, comfort, and give the sufferer a place to release their stress rather than to investigate the psychology that may be causing NVP **[18]**.
2. Dietary assessments- Dietary modifications should be a part of the interim treatment for HG and NVP. Large meals must be avoided by impacted females in favor of frequent, small meals that seem to be tasteless and low in cholesterol because foods high in fat may make it harder for the stomach to empty. Eating more protein than carbohydrates and drinking more fluids than grains may also reduce nausea. Small amounts of saline solutions, like electrolyte replacement, sports drinks are proposed **[19]**.
3. Acupressure- It has been established that acupressure at the P6 (Neiguan) on the Chinese meridians lessens patient's experiences with nausea, suggesting that it may be effective in treating HG. The pressure point's symptoms are relieved when pressure is applied to it, in accordance with the chi principle, which states that doing so inhibits aberrant energy flow. The FDA recently approved the battery-operated electrical device ReliefBand impulses stimulant tied on the wrist, and additionally, it can be used to activate the P6 location **[20]**.

II. Pharmacological treatment-

Table 1: Pharmacological therapies for NVP

Agent	Dosage
Vitamin B_6 (Pyridoxine)	10- 25 mg q8 hrs.
Doxylamine	12.5- 25 mg q8 hrs.
Secondary therapies	
Dimenhydrinate	50- 100 mg q4-6 hrs.
Diphenhydramine	25- 50 mg q8 hrs.
Hydroxyzine	50 mg q4- 6 hrs.
Meclizine	25 mg q6 hrs.
Ondansetron	4- 8 mg q6 hrs.
Metoclopramide	10 mg q6 hrs.
Promethazine	12.5- 25 mg q4- 6 hrs.

Desirable qualities of oro- dispersible film (ODF): [21-22]

1. It ought to adhere to the mouth cavity.
2. The film ought to be thin and easily melt or disintegrate in the buccal cavity.
3. It should have a lengthy therapeutic index and excellent bioavailability.
4. It must not taste bitter or have an unpleasant odor.
5. ODF needs to be temperature and humidity-resistant.

Advantages of ODFs: [23-25]

Antiemetic drug-containing oro-dispersible thin films provide several benefits compared to the market's conventional dosage forms. Those are following-

1. Without the need of water, oro-dispersible thin films provide quick, precise dosing in a secure format.
2. Faster degradation is possible due to the availability of the film's increased surface area in the oral cavity, that improves the medication's effectiveness by reducing the dose, hastening the commencement of action, and improving the onset of action.
3. ODFs can escape the fast pass hepatic because their oral mucosa is so highly vascularized.
4. It feels nice in the mouth, is simple to take, acts instantly, has increased bioavailability, and has a wide therapeutic window.

Disadvantages of ODFs: [25-26]

Oro- dispersible thin films do have several drawbacks, restrictions, and difficulties despite having many other benefits. They are following-

1. OTF packaging requires specialized tools and is more challenging than conventional packing methods.

2. Oro- dispersible thin films typically do not allow for the incorporation of greater doses, whereas tablets and capsules are quite simple to do so.
3. After taking ODFs, patients are subject to limits on what they can eat and drink.
4. Due to the co-administration of a medicine in films, it is challenging to combine more than two medications since it slows down both the rate of dissolution and the time it takes for it to disintegrate.

Preparation techniques available for oro- dispersible film:

The Fast-dissolving oral film can be made using any one of the following procedures, alone or in combination. Below is a detailed description of the various processes which are employed to create polymeric thin films: **[27-28]**

I. Solvent evaporation or casting method
II. Solid dispersion extrusion method
III. Semi- solid casting method
IV. Hot-melt extrusion method
V. Rolling method

I. Solvent casting method [27, 29]

Solvent evaporation is one of the many methods utilised to produce films, and it is practical, preferred, and unquestionably popular. This is largely because it is easy to produce and has minimal processing costs.

- Here, a drug solution is taken along with a blend of several excipients in an aqueous or hydro-alcoholic medium, such as plasticizers, polymers, and others, that are required to create the oro- dispersible film.
- The two aforementioned solutions are then combined, well mixed, and cast into a Petri plate or Petridis to be dried at 60º C.
- They are finally divided into the desired portions.

II. Solid dispersion extrusion method [30]

- The unmixable ingredients are first added to the medication during the production of the solid dispersion.
- Then, using the dies, they are formed into films.

III. Semi- solid casting method [29]

- Initially, a film-forming polymeric solution is developed in this procedure that is soluble in water.
- The finished product is then combined with a polymer solution consisting of sodium or

ammonium hydroxide that is acid-insoluble.

- In the case of the two types of polymers, when a gel mass is reached, proper amount of plasticizer has been added, the proportion of 1:4 should be maintained.
- It is then cast onto the necessary thin films using the thermally controlled barrels. As a result, this procedure is known as the semisolid casting method.

IV. Hot melting extrusion (HME) method [30-31]

In the production of ODFs, HME is a flexible technique for the development of the film **[56]**. It serves as a viable alternative to solvent casting, and is especially helpful when an organic solvent system is not required.

The following is a breakdown of HME's operational steps:

- Components are loaded via a feeder and into the evaporator.
- Blending, shredding, and kneading.
- Then molten and combined substance being flowed into the die, and
- The entire mass is processed downstream after being extruded through the die.

V. Rolling method [32]

Solution must have appropriate rheological characteristics in order to roll onto the drum in the rolling procedure that has been prepared. Rollers are used in the process of making medication and polymer suspensions in water or alcohol. Solvent evaporation occurs in suspension due to rollers. Then having dried the film, chopped into the required dimensions and forms.

Evaluation requirements:

Thickness assessment- Using a calibrated digital micrometer, the thickness of a film is measured, and the mean average is then computed from 3 readings. By chopping the film and weighing each individual film, three copies of a film's weight fluctuation are determined. Importance of thickness uniformity can be determined by the fact that it is inversely related to the film's dose accuracy **[33]**.

Folding resilience - The film is cut in one place, and it is tilted repeatedly at the exact spot until it cracks, in order to measure folding resilience. The folding resilience rating is established by how many folds at the same point the film could withstand without breaking. A film may typically be folded 100–150 times before breaking **[34]**.

Tack test- Tack describes how firmly the film sticks to the attachment after being rubbed against the strip. The dryness is also determined by this test **[34]**.

Tensile strength- The greatest tension at which a film will break is referred to as its tensile strength. In essence, this evaluation is done to assess the mechanical durability of films. The equation is beneath: **[35-36]**

$$Tensile\ strength = \frac{Load\ at\ breakage}{2aStrip\ thickness} * Strip\ width$$

Surface pH- The typical method for determining a film's pH value involves placing the developed film in a Petri dish, allowing it to become wet with distilled water, and then measuring the pH by contacting the film's surface area with a pH meter. Calculating the external pH is essential because a pH levels of either acid or base might irritate the oral mucosa **[34]**.

Swelling property- For the purpose of examining film swelling experiments, simulated saliva is used. A previously weighted mesh made of stainless steel is used to hold the film with its initial weight. After that, a film containing a mesh is submerged in a fake saliva solution. Up until there is no longer an increase in weight, the film's weight has been rising at regular, pre-determined intervals **[34, 37]**. These variables influence the degree of edoema:

$$Degree\ of\ swelling = \frac{Final\ weight\ (Wt) - Initial\ weight\ (Wo)}{Initial\ weight\ (Wo)}$$

Where,

W_0= film's weight at the moment 0

W_t= film's weight at different times t

Content uniformity- A standard assay procedure that is prescribed for each specific drug in various pharmacopoeias is used to determine a film's contents. 20 samples are used in this test, which is carried out utilising analytical methods. In accordance with USP27, the values should fall between 85% and 115%, with a standard deviation of 6% or below **[36, 37]**.

Disintegration time- For figuring out how long a film will take to disintegrate, utilize the disintegration equipment stated in authoritative pharmacopoeias. The disintegration time differs with the preparation and typically falls between 5 and 30 seconds depending on the film's composition. This test primarily employs the USP disintegration device. To calculate the film's disintegration time, there are two ways **[37-38]**.

I. Petri dish method- 2 ml of deionized water are taken in a Petri- plate, then a film is combined to it. The time consumed for the film to fully

disintegrate is referred to as the disintegration process.

II. Slide frame method- The film that is fastened to slide frames that are set on a petri- plate receives a splash of deionized water. It was remarked how long it took for the film to melt.

In-vitro dissolution test- Dissolution investigations on films are carried out using standardized approved basket or paddle apparatus. Throughout dissolution, sink conditions should be preserved. 300 ml phosphate buffer having pH of 6.8 and 0.1 N HCl are used as the media (900 ml). The rotation speed is often regulated to rpm of 50 while the heat is kept at 37 ± 0.5º C. At certain intervals, samples of the medicine are collected and examined using a UV spectrophotometer **[39]**.

REFERENCES:

[1] Gelberg, H. Pathophysiological Mechanisms of Gastrointestinal Toxicity; Elsevier: Amsterdam, The Netherlands, 2018; pp. 139–178.

[2] Thomas B, Rouf PVA, Al-Hail M, Al-Saad D, Tharannum A, *et al*. (2015) Medication used in Nausea and Vomiting of Pregnancy - A Review of Safety and Efficacy. Gynecol Obstet (Sunnyvale) 2015; 5 (2): 270-76.

[3] Vutyavanich T, Wongtra-ngan S and Ruangsri R. Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. Am J ObstetGynecol 1995; 173(3):881-4.

[4] Borsadia S, Halloran D and Osborne J. L. Quick dissolving films- A novel approach to drug delivery. Drug Deliv Technol 2003; 3:63-6.

[5] Ali MS, Vijendar C, Kumar SD and Krishnaveni J. Formulation and Evaluation of Fast Dissolving Oral Films of Diazepam. J Pharmacovigilance 2016; 4(3):210-15.

[6] Sri rekha M, Shaheda Sultana SK, Mahathi K, Parveen P, Prathima B and Seetha devi A. Formulation and Evaluation of Fast Dissolving Buccal Film Containing Isradipine Solid Dispersion. American Journal of Pharm:Tech Research 2015; 5(2):222-247.

[7] Stern, R. (2002) The psychophysiology of nausea. Acta Biol Hung 53: 589–599.

[8] Chepyala, P. and Olden, K. (2008) Nausea and vomiting. Curr Treat Options Gastroenterol 11: 135–144.

[9] Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. 2005; Hyperemesis gravidarum, a literature review. Hum Reprod Update. 11:527–539.

[10] Niebyl JR. 2010; Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med. 363:1544–1550.

[11] Furneaux EC, Langley-Evans AJ, Langley-Evans SC. 2001; Nausea and vomiting of pregnancy: endocrine basis and contribution to pregnancy outcome. Obstet Gynecol Surv. 56:775–782.

[12] Lagiou P, Tamimi R, Mucci LA, Trichopoulos D, Adami HO, Hsieh CC. 2003; Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone: a prospective study. Obstet Gynecol. 101:639–644.

[13] Depue RH, Bernstsein L, Ross RK, *et al*. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome and other maternal factors: sero-epidemiologic study. Am J Obstet Gynecol. 1987; 156:1137–1141.

[14] Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM. 1992; The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab. 75:1333–1337.

[15] Nazarpour S, Ramezani Tehrani F, Simbar M, Azizi F. 2015; Thyroid dysfunction and pregnancy outcomes. Iran J Reprod Med. 13:387–396.

[16] Glinoer D, Spencer CA. 2010; Serum TSH determinations in pregnancy: how, when and why? Nat Rev Endocrinol. 6:526–529.

[17] Kuscu NK, Koyuncu F. 2002; Hyperemesis gravidarum: current concepts and management. Postgrad Med J. 78:76–79.

[18] Deuchar N. Nausea and vomiting in pregnancy: A review of the problem with particular regard to psychological and social aspects. Br J Obstet Gynaecol. 1995; 120:6–8.

[19] Jednak MA, Shadigian Em, Kim MS, *et al*. Protein meals reduced nausea and gastric slow waves dysrhythmic activity in first trimester pregnancy. Am J Physiol. 1999; 277:855–861.

[20] Rosen T, Veciana M, Miler H, *et al*. A randomized controlled trial of nerve stimulation for relief of nausea and vomiting in pregnancy. Obstet Gynecol. 2003; 102:129–135.

[21] Bala, R., Pawar, P., Khanna, S., & Arora, S. (2013). Orally dissolving strips: A new approach to oral drug delivery system. International journal of pharmaceutical investigation, 3(2), 67–76.

[22] Irfan, M., Rabel, S., Bukhtar, Q., Qadir, M. I., Jabeen, F., & Khan, A. (2016). Orally disintegrating films: A modern expansion in drug delivery system. Saudi Pharmaceutical Journal, 24(5), 537–546.

[23] Abdulraheman, Z.S., Patel. (2015). International Journal of Universal. International Journal of Universal Pharmacy and Bio Sciences, 3(4), 93–113.

[24] Arora L, Chakraborty T. (2017). A review on new generation orodispersible films and its novel approaches. IAJPA, 7(1):7451-0.

[25] Panda, B., Dey, N. & Rao, M. E. (2012). Development of Innovative Orally Fast Disintegrating Film Dosage Forms: A Review. International Journal of Pharmaceutical Sciences and Nanotechnology, 5(2), 1666–1674.

[26] Thakur, S., & Tyagi, K. (2019). Orodispersible Films and their Patent Technology's as A Novel Drug Delivery Systems, Int. J. Pharm. Sci. Rev. Res., 58(1), 0976 – 044.

[27] Kunte S, Tandale P. Fast dissolving strips: a novel approach for the delivery of verapamil. J Pharm bioallied Sci 2010; 2:325–328.

[28] Russo E, Selmin F, Baldassari S, *et al*. A focus on mucoadhesive polymers and their application in buccal dosage forms. J Drug Deliv Sci Technol 2015; 32:113–125.

[29] Thonte SS, Pentewar RS, Bhusnure OG, Gholve SB, Gaikwad VM, Pujdekar AA. Folmulation and evaluation of oral fast dissolving film of glipizide. World J Pharm Res. 2017 May 10;6(7):1279-97.

[30] Janßen EM, Schliephacke R, Breitenbach A, *et al*. Drugprinting by flexographic printing technology – a new manufacturing process for orodispersible films. Int J Pharm 2013; 441:818–825.

[31] Dixit PR. and Puthi SP, Oral strip technology: Overview and future potential, Journal of controlled release, 2009, 94-107.

[32] Bidkar SJ, Abhishek DM and Dama GY, Development, optimization and evaluation of fast dissolving oral film, World journal of pharmacy and pharmaceutical sciences, 7(8), 2018, 1441-1445.

[33] Hariharan M, Bogue A. Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms. Drug Deliv Technol. 2009 Feb;9(2):24-9.

[34] Rekha MR, Sharma CP. Pullulan as a promising biomaterial for

biomedical applications: a perspective. Trends BiomaterArtif Organs. 2007; 20(2):116-21.

[35] Sakellariou P, Rowe R, White E. An evaluation of the interaction and plasticizing efficiency of the polyethylene glycols in ethyl cellulose and hydroxypropyl methylcellulose films using the torsional braid pendulum. IntJ Pharm. 1986; 31(1-2):55-64.

[36] Patil PC, Shrivastava SK, Vaidehi S, Ashwini P. Oral Fast Dissolving drug delivery system: A modern approach for patient compliance. Int J Drug Regulatory Affairs. 2014 Jun 1; 2(2):49- 60.

[37] Saini S, Rana AC, Gupta S. Optimization of formulation of fast dissolving films made of pullulan polymer. Int J Pharm Sci Rev Res. 2011;9(1):127-31.

[38] Laohakunjit N, Noomhorm A. Effect of plasticizers on mechanical and barrier properties of rice starch film. Starch/Staerke 2004; 56:348–356.

[39] Kunte S, Tandale P. Fast dissolving strips: A novel approach for the delivery of verapamil. J Pharm Bio Sci. 2010;2(4):325-328.