



Formulation & Evaluation of Oral Disintegration Strip (ODS) Containing Levetiracetam

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ABSTRACT

The research highlights the growing interest in buccal drug administration, emphasizing its potential for rapid onset of action and enhanced patient compliance. Focusing on formulating oral disintegration strips (ODS) of Levetiracetam, an anticonvulsant crucial for epilepsy treatment, the study employs Hydroxy Propyl Methyl Cellulose E15 (HPMC-E15) as the polymer and Propyl Ethylene glycol-400 (PEG-400) as the plasticizer.

The primary objective is to create a convenient and effective dosage form, addressing challenges associated with swallowing tablets or capsules, particularly in pediatric, geriatric, and dysphagic populations. ODS were prepared using the solvent casting method, with varying concentrations of HPMC-15 and PEG-400. Evaluation parameters included morphological properties, strip thickness, surface pH, content uniformity, disintegration time, and dissolution studies.

The findings, particularly with the optimized formulation (X5), reveal positive attributes such as transparency, tensile strength, and folding endurance. Dissolution time ranged from 3 to 4 minutes, meeting acceptable moisture content limits. The study suggests that Levetiracetam ODS hold promise for epilepsy treatment, offering a swift onset of action and potentially improving patient compliance.

The conclusion underscores that the optimized X5 formulation meets desired criteria for thickness, tensile strength, folding endurance, and dissolution time, making it a promising dosage form. The ODS technology extends beyond epilepsy, presenting opportunities for commercialization in Cosmeceuticals, Nutraceuticals, and various pharmaceutical applications. The study advocates for further research and commercialization efforts to ascertain broader acceptance and potential across diverse therapeutic areas.

Keywords: ODS, HPMC-15, PEG-400

1. Introduction

The utilization of the oral mucous membrane for drug administration is considered a promising alternative to the traditional oral route, particularly when a rapid onset of action is crucial for improved patient compliance. The buccal route, focusing on the region covered by the tongue due to its higher permeability within the buccal cavity, is preferred for such requirements. This project aimed to formulate ODS of Levetiracetam for epilepsy treatment using HPMC E-15 as a polymer at varying concentrations. The strips were prepared through the solvent casting method, with PEG-400 employed as a plasticizer. Evaluation parameters included morphological properties, strip thickness, surface pH, content uniformity, disintegration time, and dissolution studies. The outcomes indicate that the ODS containing Levetiracetam holds potential for effective and rapid treatment of epilepsy. Drug administration can be achieved through various routes for systemic pharmacological effects. While the oral route is commonly used, the administration of drugs through the buccal mucosa is a promising alternative, especially when rapid action is needed. This study focused on the formulation of Levetiracetam ODS using HPMC E-15 and PEG-400. Evaluation parameters included morphological properties, strip thickness, surface pH, content uniformity, disintegration time, and dissolution studies, revealing the potential efficacy of the developed strips for quick onset of action in the treatment of epilepsy. Levetiracetam is utilized alone or in combination with other medications to control partial-onset seizures in various age groups. The medication belongs to the anticonvulsant class, functioning by reducing abnormal excitement in the brain. This research demonstrates the potential utility of Levetiracetam ODS for efficient and rapid treatment of epilepsy, particularly in situations where prompt drug action is essential. (Balaiah et al., 2012)

The predominant method of drug administration is the oral route, and its distinctive environment presents a promising site for drug delivery. It has been recognized over the centuries that administering drugs through the oral cavity, specifically through buccal and sublingual routes, leads to rapid absorption of drug solutes. This absorption occurs through the reticulated vein beneath the oral mucosa and is subsequently transported through the facial veins, internal jugular vein, and brachiocephalic vein, ultimately draining into the systemic circulation. Consequently, drug administration through the oral cavity can be exploited to bypass the hepatic first-pass metabolism. The oral mucosal cavity regions exhibit enhanced drug absorption into the systemic circulation. The oral mucosa is characterized by a rich blood supply and increased permeability. This method of administration has garnered significant

acceptance, particularly among dysphagic patients. Furthermore, the oral mucosa displays potential tolerance to allergens, attributed to the virtual absence of Langerhans cells. It is essential to note, however, that not all drugs can be administered through the oral mucosa due to the specific characteristics of the oral mucosa and the physicochemical properties of the drugs (Vaishali & Bhagyashri, 2015).

The mucous membrane within the oral cavity represents a potential site for the development of sustained and controlled drug delivery systems, garnering interest from both medical practitioners and manufacturers. Among all available dosage forms, oral solid dosage forms constitute approximately 60%. Challenges such as dysphagia in patients, lower bioavailability, and prolonged onset times often prompt medical practitioners and manufacturers to consider parenteral and liquid oral alternatives. However, the issues of precise dosing in liquid oral formulations (e.g., syrups, suspensions, emulsions, etc.) and the discomfort associated with parenteral drug administration contribute to patient non-compliance.

Within the oral cavity, specific sites for targeted drug delivery include the tongue, sublingual area, periodontal region, gum, and buccal region. The oral route stands out as the most popular means of administering therapeutic agents due to its cost-effectiveness and ease of administration, resulting in high levels of patient compliance. Tablets and capsules are the predominant forms of oral solid dosage, yet challenges arise, particularly for geriatric patients who may encounter difficulties in swallowing, leading to non-adherence to prescribed medication. Notably, approximately 35% of the general population is affected by difficulties in swallowing, also known as dysphagia (kumar Vishwakarma & Deshkar Siddhayu, 2015).

The ODS drug delivery system is a preferred dosage form, chosen for its ease of transportation and specifically designed for drugs with extensive manufacturing requirements and enhanced patient compliance. This innovative formulation is particularly suitable for drugs characterized by first-pass metabolism, low doses, and those intended for geriatric, pediatric, and bedridden patients who may experience difficulties in swallowing conventional oral dosage forms. The ODS is a solid dosage form designed to disintegrate or dissolve within one minute when placed in the mouth, without the need for drinking or chewing. This novel delivery system addresses the challenges posed by traditional oral dosage forms and offers advantages such as enhanced bioavailability, especially beneficial for patients who face difficulties in swallowing. The ODS has gained popularity as a new delivery system due to its ease of administration and the potential for a sudden onset of drug action when taken through the sublingual route (Panpaliya et al., 2021). The oral route remains the most favored method for drug delivery due to its numerous advantages over alternative administration routes. However, advancements in oral drug delivery systems are still required to address certain limitations, particularly in specific patient populations such as geriatric, pediatric, and dysphasic individuals who encounter challenges in swallowing or chewing solid dosage forms.

Structurally, the oral cavity commences at the vermilion border, which delineates the transition between the skin and lips. The buccal region, a component of the oral cavity, is bordered anteriorly and laterally by the lips and cheeks, posteriorly and medially by teeth and/or gums, and superiorly and inferiorly by the mucosal reflections from the lips and cheeks to the gums. The hard palate forms the roof of the mouth. The buccal mucosa receives its blood supply from the Maxillary artery (Patil et al., 2014). The oral cavity encompasses a surface area of approximately 100 square centimeters, with one-third of this area being occupied by the buccal mucosa, characterized by a thick layer of epithelium measuring about 0.5mm. The structure of the oral mucosa comprises multiple layers, with the outermost layer identified as stratified squamous epithelium. Beneath this layer, there is a basement membrane, a lamina propria, and the innermost layer referred to as submucosa. The topmost layer of the oral mucosa, the stratified squamous epithelium, shares similarities with epithelial tissues found elsewhere in the body. This squamous epithelium consists of a mitotically active basal cell layer. The complete turnover of the oral mucosa's epithelium takes approximately 5-6 days (kumar Vishwakarma & Deshkar Siddhayu, 2015). The thickness of the oral mucosa exhibits significant variation across different regions of the oral cavity. The buccal mucosa is estimated to have a thickness ranging from approximately 500 to 800 micrometers (μm). In contrast, other regions such as the hard palate, soft palate, ventral tongue, gingiva, and floor of the mouth have a comparatively thinner mucosal layer, with thicknesses ranging from about 100 to 200 μm (Curatolo, 1987). The mucosal layers within the oral cavity exhibit varying compositions across different sites. In the gingiva and hard palate, the mucosal layers are composed of keratin, similar to the composition of the epidermis. This keratinized layer, comprising ceramides and acyl ceramides, contributes to the barrier function of the mucosa. This barrier function is crucial for protection and integrity. On the other hand, the mucosal layers of the buccal region, sublingual area, and soft palate are devoid of keratin. Consequently, these regions lack the keratinized layer and are relatively impermeable to water. The absence of keratin in these areas affects their permeability characteristics, distinguishing them from the keratinized mucosa found in the gingiva and hard palate (Pachauri et al., 2023). Indeed, the layers of the sublingual and buccal regions are characterized by the presence of bipolar lipids, specifically neutral lipids such as cholesterol sulfate and glucosyl ceramides. These lipid components contribute to the overall composition of the mucosal layers in these non-keratinized epithelial regions. It has been observed that non-keratinized epithelial layers, such as those in the sublingual and buccal regions, exhibit higher permeability to water when compared to keratinized epithelial layers. This increased permeability is attributed to the absence of the protective keratin layer, allowing for a more direct interaction with water and other substances (Patel et al., n.d.).

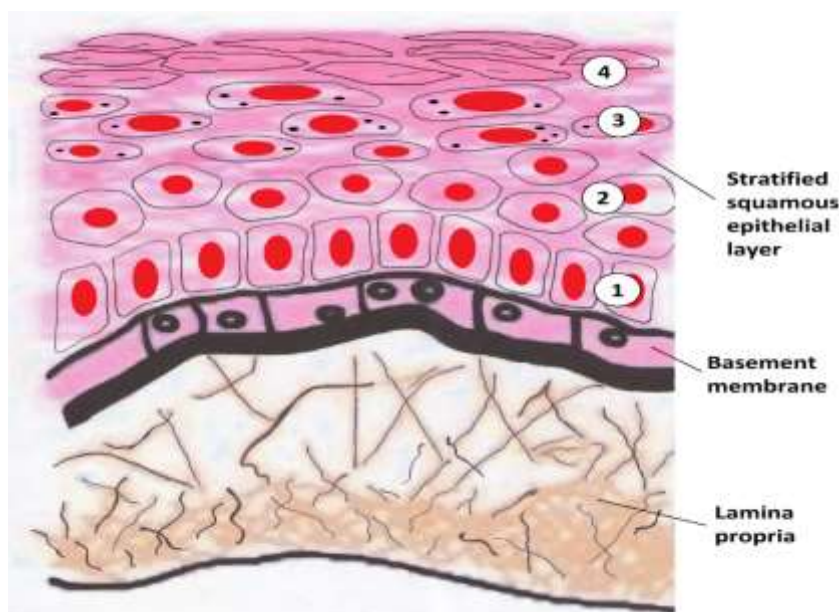


Fig. 1 - Oral mucosa membrane

The current study assumes that the formulation and evaluation of ODS containing Levetiracetam not only enhance the rate of drug delivery but also increase in the potency of the drug.

1.1 Composition of Oromucosal cells:



Fig. 2 - ODS Strip

The mucosal cells of the oral cavity are primarily composed of proteins and carbohydrates. This composition imparts an adhesive nature to the cells, facilitating their movement relative to one another with reduced friction (*Orally Disintegrating Strips (ODS) Convenience of Liquid Dosage Form and Dose Accuracy of Solid Dosage Form*, n.d.). Unlike other parts of the body where the synthesis and secretion of mucus are primarily carried out by goblet cells, in the oral cavity, this process is primarily performed by both minor and major salivary glands. The mucus produced in the oral cavity is of significance as it plays a crucial role in the bioadhesion of mucoadhesive drug delivery systems (Hancock, n.d.). Additionally, research indicates that approximately 70% of the aggregate mucin content is localized within saliva, originating from the minor salivary glands (Iorgulescu, 2009). The oral cavity contains three pairs of salivary glands: sublingual, submandibular, and parotid. Saliva, originating from these glands, comprises both organic (1%) and inorganic components. Salivary amylase, a digestive enzyme present in saliva, plays a crucial role in the metabolism of starch within the oral cavity. The chemical composition of saliva closely resembles that of blood plasma. Saliva's pH ranges from 5 to 7. In a healthy adult, the daily production of saliva is approximately 1-2 liters, providing an ample quantity to hydrate orally administered dosage forms. The water-rich environment of the mouth prompts manufacturers to incorporate hydrophilic agents as vehicles in oral drug delivery systems (Kubala et al., 2018).

1.2 Permeability:

The permeability of the oral mucosa falls between that of the skin and the intestinal membrane, with a 4-4000 times higher permeability compared to the epidermis. Significant variations in permeability exist among different regions of the oral cavity, attributable to the diverse structures and functions of these regions. To enhance drug absorption from oral dosage forms within the oral cavity, permeation enhancers are employed (Squier, 1991). The following are examples of permeation enhancers:

- Aprotinin
- Cetylpyridinium chloride
- Cyclodextrin
- Menthol
- Sodium glycodeoxycholate
- Sodium taurodeoxycholate

- Azone
- 23-lauryl ether
- Dextran sulfate

2. Oral Disintegrating Strips (ODS)

ODS are defined as orally administered dosage forms that utilize film-forming polymers, typically hydrocolloids, plasticizers, and Active Pharmaceutical Ingredients (APIs) along with other additives. When placed on the tongue, ODS rapidly hydrate, adhere, and dissolve in the oral cavity, facilitating swift local and systemic drug actions. The evolution of oral drug delivery systems has progressed from conventional tablets/capsules to modified-release tablets and then to orally disintegrating tablets, such as wafers. The most recent and modern iteration of this dosage form is ODS. Essentially, ODS can be described as thin strips of stamp size containing APIs. Both pediatric and geriatric populations have demonstrated equal acceptance of this dosage form, attributed to the portability and convenient dosing offered by ODS (Irfan et al., 2016). Several marketing research firms, including Root Analysis and Technology Catalysts, have conducted forecasts for the emerging market of Orally Disintegrating Strips (ODS). According to their projections, the market for drug products in ODS was valued at \$500 million in 2007, escalating to \$2 billion in 2012, and further surging to \$15 billion in 2015. The forecasts suggest a sustained upward trajectory in global growth trends for ODS, with expectations extending to the year 2025 (*PDF Orally Disintegrating Strips (ODS) Convenience of Liquid Dosage Form and Dose Accuracy of Solid Dosage Form*, n.d.).

2.1 ODS dosage forms gives some distinct advantages over other conventional oral formulations (Sevinç Özakar & Özakar, 2021).

- Orally disintegrating tablets (ODS) exhibit superior durability, rapid dissolution, and stability compared to other oral dosage forms.
- Each ODS film is formulated to uniformly distribute a precise quantity of drugs, enhancing dosage accuracy in comparison to liquid formulations.
- The inherent ease of administration and intuitive nature of ODS contribute to improved patient compliance and precise drug dosing.
- ODS, with its capacity for rapid dissolution without the need for water, offers an alternative for patients unable to swallow or experiencing nausea, such as those undergoing chemotherapy.
- ODS enables continuous drug administration, particularly beneficial for drugs with a short biological half-life.
- Rapid disintegration and dissolution within seconds in the oral cavity are facilitated by the accessibility of a larger surface area in ODS.
- The substantial surface area (1-20 cm) of ODS allows swift hydration by saliva, leading to rapid disintegration, dissolution, and direct entry into the systemic circulation, bypassing first-pass hepatic metabolism and enhancing drug bioavailability.
- By bypassing the first-pass effect, ODS administration significantly reduces drug doses, potentially decreasing associated side effects.
- ODS eliminates the need for parenteral shots, thereby avoiding associated risks, pain, and inconvenience.
- ODS protects drug molecules from the acidic stomach environment.
- The manufacturing of ODS does not necessitate specialized setups.
- ODS delivery can be terminated at any time as needed.
- Noninvasive administration makes ODS more widely accepted.
- ODS can serve as an alternative for patent life extension.

2.2 ODS Technologies and Commercialized Products.

Following breath fresheners, the Over-the-Counter drugs (OTC) and Nutraceuticals market emerged as the initial adopter of Orally Disintegrating Film (ODF) technology, incorporating active molecules like herbal and non-herbal extracts and vitamins. Notably, Pfizer introduced Listerine® PocketPaks® in 2001 as a well-known ODF product targeting bad breath. Additionally, Novartis introduced Theraflu® and Triaminic® brands in ODF form, further expanding the application of this technology in the pharmaceutical market (Slavkova & Breitreutz, 2015).

2.3 Mechanism of action

- The delivery system of Orally Disintegrating Strips (ODS) involves straightforward placement on the tongue or within the buccal cavity.
- Upon contact, the ODS rapidly becomes wetted by saliva, facilitated by the presence of hydrophilic agents within the film.
- Subsequently, the film undergoes hydration and dissolution, thereby releasing the medication or active constituents incorporated within.

- The dissolved drug molecules are then readily available for absorption via the oral mucosa, facilitating oromucosal absorption.

The delivery system of *ODS* is very simple, it has to be placed on a patient's tongue or anywhere in oral cavity. Instantly, hydrophilic polymers added in *ODS* will wet the Strips by saliva, the film rapidly hydrates and start dissolving to release the API's incorporated in films. Thereafter drug molecules are freely available for absorption in oral cavity (Ketul et al., 2013). The *ODS* technology exhibits the potential for delivering various classes of Active Pharmaceutical Ingredients (APIs). Nevertheless, the size constraints of *ODS* impose limitations on the incorporation of high doses of APIs. Typically, APIs ranging from 5-30% w/w and multivitamins up to 10% w/w of the *ODS* weight can be effectively incorporated, ensuring minimal dissolution time (*Orally Disintegrating Strips (ODS) Convenience of Liquid Dosage Form and Dose Accuracy of Solid Dosage Form*, n.d.). The distribution of drugs within Orally Disintegrating Strips (*ODS*) is contingent upon their solubility characteristics. Water-soluble drugs are integrated either in a dissolved state or as solid solutions, while water-insoluble drugs are uniformly dispersed throughout the film. In large-scale manufacturing, achieving even distribution of insoluble drugs in water-miscible polymers becomes crucial. Depending on the desired release profile, drugs can be incorporated in forms such as micronized, milled, or as nanoparticles (Zhang et al., 2018).

2.4 Ideal characteristics of drugs.

- Drugs utilized in Orally Disintegrating Strips (*ODS*) should either be devoid of a bitter taste, or if inherently bitter, effective measures for taste masking should be employed.
- Selected drugs must exhibit stability in both saliva and water environments.
- The dosage of drugs should be minimized, ideally not exceeding 40 mg.
- Drugs are preferable when partially unionized within the pH range of 5-7.
- The chosen drugs should possess the capability to permeate the oral mucosa for optimal effectiveness in *ODS* delivery.

2.4.1 Water soluble Polymers

Numerous polymers are at disposal for the formulation of Orally Disintegrating Strips (*ODS*). The desired strips can be achieved through the use of polymers either individually or in combination. The prepared *ODS* must exhibit sufficient toughness to withstand mechanical stresses during transportation. The robustness of *ODS* is contingent on the type and quantity of polymers employed in the formulation. *ODS* should possess the crucial property of rapid disintegration, ensuring the swift release of Active Pharmaceutical Ingredients (APIs) within seconds. Water-soluble polymers play a pivotal role, serving as essential agents that provide the foundational platform for *ODS* (Jagtap et al., 2012).

2.4.1.1 Ideal properties of water-soluble polymers.

- The material should be non-toxic, non-irritating, and free from leachable properties.
- It should readily hydrate and disperse.
- The material should demonstrate satisfactory peel, shear, and tensile strengths.
- It should be cost-effective and readily accessible.
- A good shelf life is essential.
- It should not contribute to the occurrence of secondary infections in the oral cavity.

2.4.2 Plasticizers

Plasticizers play a crucial role in the formulation of Orally Disintegrating Strips (*ODS*) by enhancing flexibility and reducing brittleness. They effectively lower the glass transition temperature, significantly improving the properties of the strips. Commonly used plasticizers include Glycerol, Propylene glycol, low molecular weight polyethylene glycols, and phthalate derivatives such as dimethyl, diethyl, and dibutyl phthalate. Citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin, and castor oil are also frequently employed. However, improper use of plasticizers can lead to issues such as cracking, splitting, and peeling of the films. Moreover, it has been observed that the absorption rate of drugs may be influenced by the use of specific plasticizers (Eslami et al., 2023).

2.4.3 Surfactants

Surfactants, also recognized as wetting, solubilizing, or dispersing agents, are incorporated into formulations to facilitate the dissolution and rapid release of Active Pharmaceutical Ingredients (APIs) in Orally Disintegrating Strips (*ODS*). Common examples of surfactants include sodium lauryl sulfate, benzalkonium chloride, and tweens. An especially noteworthy surfactant is poloxamer 407. Their presence aids in improving the solubility and dispersion of components in the *ODS*, ensuring efficient and instant release of APIs (Jin et al., 2021).

2.4.4 Sweetening agents

Sweeteners play a crucial role in Orally Disintegrating Film (ODF) formulations, designed to disintegrate and dissolve in the oral cavity. Both natural and synthetic sweeteners are employed to enhance the palatability of oral dosage forms, a particularly significant factor in formulating for pediatric patients. Commonly used sweeteners include sucrose (derived from cane or beet in liquid or dry form), dextrose, fructose, glucose, liquid glucose, maltose, saccharin, cyclamate, aspartame, acesulfame-K, sucralose, alitame, neotame, and Rebiana (a herbal sweetener derived from the plant *Stevia rebaudiana*). Additionally, some sweeteners are included in formulations to impart desirable mouthfeel and cooling sensations, such as polyhydric alcohols like sorbitol, mannitol, isomalt, and maltitol, which can be used in combination (Humaid, 2018).

2.4.5 Saliva stimulating agents

Saliva stimulants are utilized in Orally Disintegrating Strips (ODS) formulations to augment the rate of saliva production in the oral cavity, facilitating the rapid disintegration and dissolution of the strips. Typically, food-grade acids employed for culinary purposes serve as effective saliva stimulants. Commonly used stimulants include citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid.

Flavoring, coloring, stabilizing, and thickening agents also play essential roles in ODS formulations. Taste preferences are influenced by age, with younger generations favoring flavors like fruit punch and raspberry, while geriatric patients may prefer mint or orange flavors. The choice of flavors is also influenced by the type of drugs incorporated in ODS. Examples of flavorings include peppermint oil, cinnamon oil, spearmint oil, nutmeg oil, vanilla, cocoa, coffee, chocolate, citrus, apple, raspberry, cherry, and pineapple.

Pigments such as titanium dioxide or FD&C-approved coloring agents are added to ODS formulations, typically not exceeding concentration levels of 1% w/w. These pigments contribute to the visual appeal of the strips.

Stabilizing and thickening agents are introduced into film formulations to enhance viscosity and ensure consistent dispersion of ODS. Examples of such agents include xanthan gum, locust bean gum, carrageenan, and cellulosic derivatives (Hemavathy et al., 2022).

2.5 Role of Excipients in Formulation of ODS

Hydroxypropyl Methylcellulose (HPMC) serves a dual purpose in Orally Disintegrating Strips (ODS) formulations by extending dissolution time and facilitating rapid drug release within seconds. Additionally, HPMC contributes to the overall strength and integrity of the strip.

Polyethylene Glycol 400 (PEG-400) plays a crucial role in enhancing the flexibility and reducing the brittleness of ODS. It also contributes to improving the transparency of the strip.

Sucralose is incorporated as a sweetening agent to enhance the palatability of ODS strips.

Ethanol serves as a solvent in the formulation process.

Peppermint oil functions as a saliva-stimulating agent, aiding in the disintegration of the strip.

Amaranth is utilized as a coloring agent to impart an elegant appearance to the ODS strip.

3. PRODUCTION AND MANUFACTURING OF ODS

Manufacturing and production of *ODS* can be done by using any of the process mentioned below,

3.1 Solvent casting

The solvent casting process for the production of Orally Disintegrating Strips (ODS) involves several steps:

- Solvent selection

Water-soluble excipients are dissolved in water.

Other solvent-soluble excipients are dissolved in an appropriate organic solvent

- Drug Addition

The drug, in this case, levetiracetam, is then added to the solution.

The solution is stirred thoroughly to ensure proper mixing and the formation of a homogeneous solution.

- Casting

The homogenized solution is then cast into a suitable mold, often a petri dish.

The casting process involves pouring the solution into the dish, spreading it evenly to achieve a uniform thickness.

- Drying

The casted solution is allowed to dry.

During the drying process, the solvents evaporate, leaving behind a solidified film or strip.

The resulting Orally Disintegrating Strips are designed to dissolve or disintegrate rapidly in the oral cavity, providing a convenient dosage form for administration. The solvent casting method allows for the incorporation of various excipients and the drug in a controlled and homogenous manner, contributing to the overall quality and performance of the ODS.

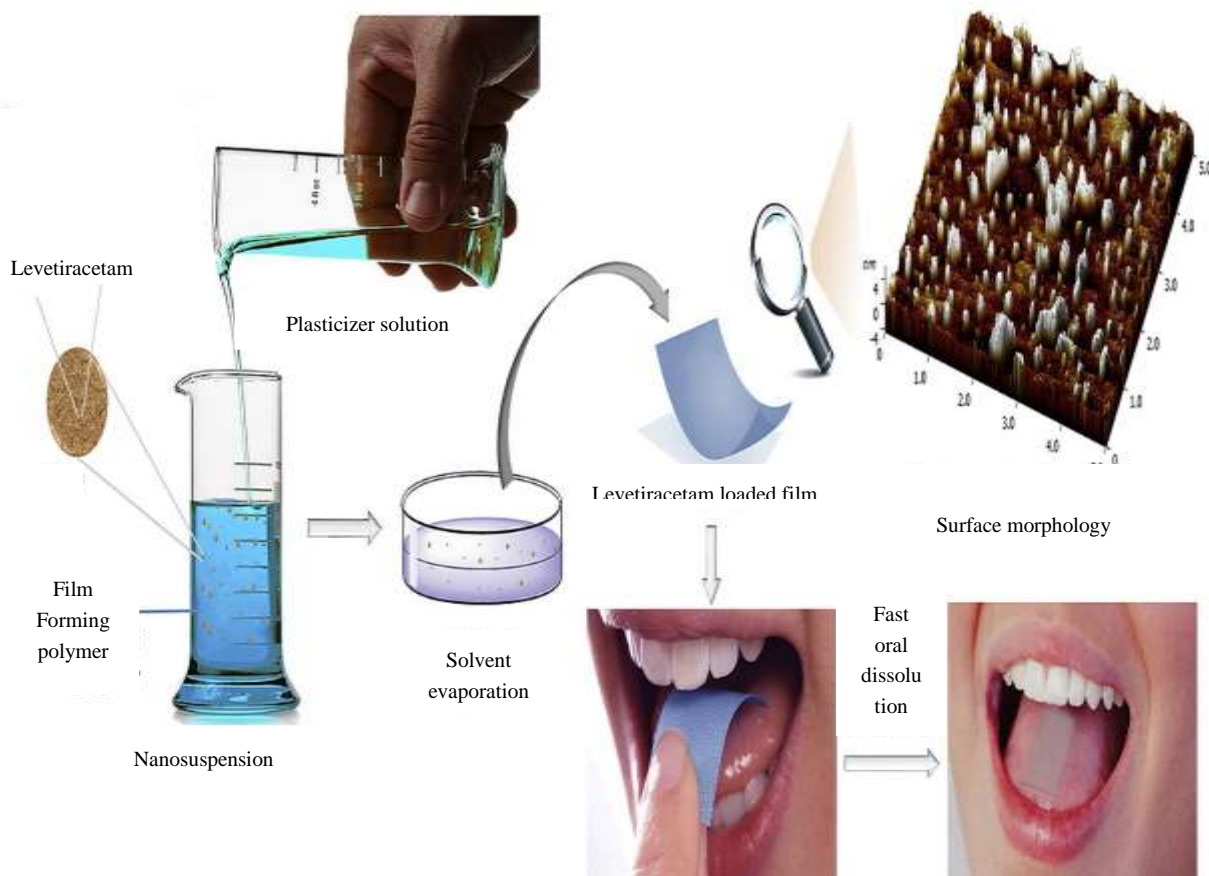


Fig. 3 - Solvent Casting Method

3.2 Semisolid Casting

In the described process of Orally Disintegrating Strips (ODS) production:

- Polymer Mixture

Water-soluble polymers are combined with acid-insoluble polymers to create a viscous and homogeneous solution.

The choice of polymers may depend on their solubility characteristics and the desired properties of the ODS.

- Coating

The viscous and homogenous polymer solution is coated onto a non-treated casting film.

The non-treated casting film serves as a substrate for the ODS.

- Sonication

After coating, sonication is employed.

Sonication involves the use of ultrasonic vibrations to aid in the uniform spreading and distribution of the polymer solution on the casting film.

- Ration Maintenance

It's emphasized that a specific ratio of 1:4 should be maintained, with acid-insoluble polymer to water-soluble polymer.

This ratio is likely optimized to achieve the desired properties and characteristics of the ODS.

This production process ensures the creation of ODS with controlled composition and uniformity, ultimately influencing the performance and quality of the final dosage form.

3.3 Hot melt extrusion

The described process of Orally Disintegrating Strips (ODS) production involves the following steps:

- Drug and carrier Mixing

Drugs are combined with a carrier in solid form.

The carrier serves as a medium to facilitate the processing and formation of the strips.

- Extrusion

The solid mixture of drug and carrier is then passed through an extruder.

Within the extruder, heaters are employed to melt the mixture.

The application of heat results in the transformation of the solid mixture into a molten state.

- Shaping Strips

The molten mixture is shaped into strips using dies.

Dies are molds or tools that give the strips their final form and dimensions.

This process of extrusion and shaping allows for the creation of Orally Disintegrating Strips in a continuous and controlled manner. The choice of carriers and the extrusion conditions can impact the properties of the strips, ensuring they meet the desired characteristics for rapid dissolution or disintegration in the oral cavity.

3.4 Rolling process

The described process of Orally Disintegrating Strips (ODS) production involves several steps:

- Premixing

Prepare a premix containing a film-forming polymer, polar solvent, and other additives, excluding the drug.

This premix serves as the base for the ODS formulation

- Master Batch Preparation

Add the premix to a master batch feed tank

- Metering and Mixing

Use a first metering pump and control valve to feed the premix to either the first or second mixer, or both.

Incorporate the required amount of the drug into the desired mixer.

Blend the drug with the master batch premix to achieve a uniform matrix.

- Feeding to pan

A specific amount of the uniform matrix is fed to the pan through a second metering pump.

The pan is the platform where the film formation process takes place.

- Film Formation

The film is formed on a substrate within the pan.

The substrate can be a material that supports the formation and handling of the ODS.

- Drying

The formed film is carried away via a support roller.

Drying of the film occurs, typically using bottom drying methods.

This comprehensive process results in the production of Orally Disintegrating Strips, where the film serves as the carrier for the drug and other essential components, providing a convenient dosage form for rapid dissolution or disintegration in the oral cavity.

Components of Oral Disintegration Strip

Table 1: Composition of Mouth Oral Disintegration Strip

Contents	Percentage (%)
Drugs	5% to 30% w/w
Water soluble polymer	45% w/w
Plasticizers	0-20% w/w
Surfactants	q.s.
Sweetening agent	3 to 6 % w/w
Saliva stimulating agent	2 to 6% w/w
Fillers, colors, flavors etc.	q.s.

These percentages provide a flexible range for formulating Mouth Oral Disintegration Strips, allowing adjustments based on specific requirements and considerations. The water-soluble polymer matrix plays a key role in achieving immediate dissolution, and plasticizers are important for controlling mechanical properties.

4. Preparation of Oral Disintegration Strip by solvent casting method:

The preparation of Fast Dissolving Film of Levetiracetam using Hydroxypropyl Methylcellulose (HPMC) E15 as a polymer by the solvent casting method involves the following steps:

4.1 Polymer Dissolution

HPMC E15 is dissolved in 8 ml of water using a magnetic stirrer.

The stirring process ensures uniform dissolution of the polymer in the water.

4.2 Sucralose Dissolution

Sucralose is separately dissolved in the remaining 2 ml of hot water.

The use of hot water aids in the dissolution of sucralose.

4.3 Drug Dissolution

The drug, Levetiracetam, is dissolved in the polymer solution.

This step incorporates the active pharmaceutical ingredient into the polymer matrix.

4.4 Plasticizer Addition

A plasticizer is added to the polymer solution.

The plasticizer enhances the flexibility and mechanical properties of the film.

4.5 Sweetener Solution Addition

The solution containing the dissolved sucralose (sweetener) is added to the polymer solution.

This step imparts a sweet taste to the film.

4.6 Deaeration

The combined solution is allowed to stand for 30 minutes to allow deaeration.

Deaeration helps remove any trapped air bubbles in the solution.

4.7 Casting

The solution is cast onto a Petri dish.

The casting process involves spreading the solution evenly to form a thin film.

4.8 Drying

The casted solution is allowed to dry at room temperature for 24 hours.

Drying results in the solidification of the film

4.9 Cutting

The dried film is removed and cut into the required size of 3 x 2 cm².

Cutting produces individual units of the fast-dissolving film.

The final product is a ODS of Levetiracetam, which is designed to dissolve rapidly when exposed to saliva, providing a convenient oral dosage form.

Table 2: Formulation Batches of ODS of Levetiracetam

Formulation Batches	Drug (mg)	HPMC-E15 (mg)	PEG-400 (mg)	Peppermint oil (ml)	Sucralose (mg)	Water (ml)	Ethanol (ml)
X1	15 mg	400 mg	100 mg	0.1 ml	20 mg	10 ml	10 ml
X2	15 mg	400 mg	100 mg	0.1 ml	22 mg	10 ml	10 ml
X3	15 mg	500 mg	100 mg	0.1 ml	24 mg	10 ml	10 ml
X4	15 mg	550 mg	110 mg	0.1 ml	25 mg	10 ml	10 ml
X5	15 mg	600 mg	125 mg	0.1 ml	26 mg	10 ml	10 ml
X6	15 mg	500 mg	125 mg	0.1 ml	27 mg	10 ml	10 ml
X7	15 mg	600 mg	140 mg	0.1 ml	28 mg	10 ml	10 ml
X8	15 mg	650 mg	150 mg	0.1 ml	30 mg	10 ml	10 ml

5. Evaluation of Oral Disintegration Strip.

5.1 Thickness test:

The thickness of the ODS is a critical parameter that can impact the accuracy of the dose. To measure this property, micrometer screw gauges are utilized at various strategic locations on the film. This measurement process helps ensure the uniformity of thickness throughout the film.

Procedure:

- Micrometer Screw Gauges:

Micrometer screw gauges are precision instruments designed for accurate measurement of small dimensions.

They typically consist of a calibrated screw mechanism, allowing precise measurement of thickness.

- Strategic Measurement Locations:

Measurements are taken at different strategic locations on the fast-dissolving film.

Strategic locations may include various points across the film to ensure representative measurements.

- Uniformity Check:

The measurements are compared to assess the uniformity of the film's thickness.

Ensuring uniform thickness is crucial for maintaining the accuracy of the dose across different sections of the film.

- Quality Assurance:

The measurements serve as a quality control parameter, providing information about the film's manufacturing consistency.

Consistent thickness is vital to achieving uniform drug distribution and dissolution characteristics.

By employing micrometer screw gauges and conducting measurements at different locations, the film's thickness can be thoroughly evaluated, contributing to the quality and accuracy of the final product. This quality control step is particularly important in pharmaceutical manufacturing to meet regulatory standards and ensure the efficacy of the dosage form.

5.2 Tensile strength:

The tensile strength of a material, including a film, is indeed a crucial mechanical property. It represents the maximum stress that the material can withstand before breaking. The formula you've provided for calculating tensile strength is correct:

Tensile strength = Load at failure × 100 / Strip thickness × film width

Procedure:

- Load at Failure:

The force applied to the material at the point of breaking during a tensile test.

- Strip Thickness:

The thickness of the film, typically measured in millimeters

- Film Width:

The width of the film, also measured in millimeters.

The result of this calculation is expressed in units of stress, commonly measured in megapascals (MPa) or newtons per square millimeter (N/mm²). Tensile strength is an important parameter in assessing the mechanical integrity and performance of the film, especially in applications where the film needs to withstand stress or stretching forces.

5.3 Folding endurance:

The property you're describing, where the film is folded repeatedly until it breaks, is often referred to as "fold endurance" or simply "fold strength." Fold endurance is a measure of the film's ability to withstand repeated folding without breaking.

The procedure to determine fold endurance involves the following steps:

- Folding:

The film is folded at the same place repeatedly until it breaks.

- Counting Folds:

The number of folding cycles required to cause the film to break is recorded.

The result, the number of folding cycles or the total number of folds until failure, represents the fold endurance of the film. This property is important in applications where the film may undergo repeated bending or folding during handling or use.

Fold endurance is particularly relevant for flexible materials, such as films, where durability and resistance to wear and tear are essential considerations. It provides valuable information about the material's mechanical robustness in dynamic conditions.

5.4 Dissolution test:

The property you are describing, where the dissolution rate of a drug from a film is measured using a standard basket or paddled apparatus, is commonly referred to as the "dissolution rate" or "in vitro dissolution." This testing is crucial for assessing how effectively a drug is released from its dosage form.

Procedure:

- Dissolution Apparatus:

A standard dissolution apparatus, such as the basket or paddle apparatus, is used for testing. These apparatuses are defined by pharmacopoeias, outlining their specifications and usage.

- Selection of Medium:

The selection of the dissolution medium is based on factors like the sink condition and the highest dose of the drug.

Sink conditions ensure that the concentration of the drug in the dissolution medium remains low, preventing saturation and maintaining a constant rate of dissolution.

- **Testing Procedure:**

The film or dosage form is placed in the dissolution apparatus.

The apparatus is then immersed in the dissolution medium.

- **Dissolution:**

The drug is released from the film into the dissolution medium over a specified period.

The dissolution apparatus mimics the conditions the dosage form would encounter in the human body.

- **Sampling:**

Samples of the dissolution medium are withdrawn at predetermined time intervals.

- **Analysis:**

The concentration of the drug in each sample is analyzed, often using techniques like spectrophotometry or chromatography.

- **Dissolution Profile:**

The results are used to generate a dissolution profile, showing the percentage of drug released over time.

In the pharmaceutical industry, this dissolution testing is a crucial step in ensuring the effectiveness and consistency of drug release from various dosage forms, including films. It helps in establishing the dissolution characteristics of the formulation, which is important for regulatory compliance and ensuring the drug's therapeutic efficacy.

5.5 Moisture Content:

The procedure you've described outlines a method for determining the percentage moisture loss of films over a specified period. Here's a breakdown of the steps:

Procedure:

- **Film Preparation:**

Films of a specified area ($2 \times 3 \text{ cm}^2$) are cut from the material under investigation.

- **Initial Weighing:**

The cut films are accurately weighed using an electronic balance.

The initial weight is recorded.

- **Room Environment Exposure:**

The films are placed in a room environment for a designated period, in this case, 72 hours.

- **Final Weighing:**

After the 72-hour exposure, the films are taken out and weighed again.

The final weight is recorded.

- **Calculation of Percentage Moisture Loss:**

The percentage moisture loss is calculated using the formula:

Percent moisture loss = $(\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100$.

This formula quantifies the percentage change in weight, representing the loss of moisture over the specified duration. Monitoring moisture loss is crucial in various industries, especially in the pharmaceutical and packaging sectors, where the stability and quality of materials are highly dependent on their moisture content. This testing helps ensure that the films maintain their desired properties over time, as excessive moisture loss or gain can affect product performance.

6. Packaging of ODS

Preserving the integrity of pharmaceutical products, including Orally Disintegrating Strips (ODS), is indeed crucial, and proper packaging plays a vital role in achieving this goal. Here are some points related to packaging considerations for ODS:

6.1 Importance of Packaging:

Packaging is essential for protecting the dosage form during manufacturing, transportation, and storage.

It helps prevent contamination, maintain product stability, and ensures the safety of the product.

6.2 Special Care for ODS:

Orally Disintegrating Strips require special care during manufacturing and production to maintain their delicate nature, rapid dissolution characteristics, and prevent any damage.

6.3 Single Packaging Requirement:

ODS typically requires single packaging, ensuring individual protection for each strip.

Single packaging helps maintain the hygiene and integrity of each unit.

6.4 Commonly Used Packaging - Aluminum Pouch:

Aluminum pouches are commonly used for ODS packaging.

Aluminum provides a barrier against moisture, light, and other environmental factors that could affect the stability of the strips.

6.5 Other Packaging Formats:

Foil, paper, or plastic pouches are alternative packaging options.

Blister cards with multiple units may also be used for packaging ODS.

Choosing the right packaging material is critical to ensuring the effectiveness and stability of the ODS throughout its lifecycle. Aluminum pouches, due to their barrier properties, are often preferred for protecting the strips from external factors. The selection of packaging depends on factors such as the specific requirements of the ODS formulation, regulatory considerations, and compatibility with the intended use.

7. Result:

The results of the evaluation parameters for eight different formulations are summarized below:

Table 3: Evaluation Parameters (Transparency, Tensile Strength, Folding Endurance, Surface pH)

Formulation Batch	Transparency	Tensile Strength Kg/mm ²	Folding Endurance	Surface pH
X1	Good	7.48	184	6.72
X2	Poor	9.20	175	6.59
X3	Good	8.93	164	6.82
X4	Good	7.54	154	6.81
X5	Best	10.90	164	6.97
X6	Best	10.51	169	6.56
X7	Good	8.20	178	6.72
X8	Good	11.15	172	6.87

Table 4: Evaluation Parameter for Thickness (μm)

Sr. No.	Formulation Batch	Thickness (μm)
1	X1	89
2	X2	120
3	X3	80
4	X4	150
5	X5	70
6	X6	95
7	X7	165
8	X8	125

Table 5: Evaluation Parameter for Dissolution Test

Sr. No.	Formulation Batch	Weight (gm)	Dissolution Time (min)
1	X1	0.563	3.5
2	X2	0.659	3.8
3	X3	0.459	3.2
4	X4	0.746	4
5	X5	0.456	3
6	X6	0.580	3.7
7	X7	0.759	4.3
8	X8	0.684	3.9

Table 6: Evaluation Parameter for Moisture Content (%)

Sr. No.	Formulation Batch	Moisture Content (%)
1	X1	0.53
2	X2	0.60
3	X3	0.87
4	X4	0.80
5	X5	0.65
6	X6	0.51
7	X7	0.52
8	X8	0.58

The formulations demonstrate a range of characteristics, with variations in transparency, tensile strength, folding endurance, surface pH, thickness, dissolution time, and moisture content. The data provides valuable insights into the performance of each formulation batch, aiding in the optimization and selection of the most suitable formulation for the intended application.

8. CONCLUSION

In conclusion, the oral disintegration strip incorporating Levetiracetam emerges as a viable and clinically suitable option for managing epilepsy. The key takeaways from the results support the following conclusions:

8.1 Clinical Suitability:

The oral disintegration strip is deemed appropriate for clinical use in epileptic treatment, offering the advantage of a quicker onset of action, which is crucial in conditions requiring rapid therapeutic effects. Additionally, the convenience of administration aligns with patient preferences and ease of use.

8.2 Optimal Formulation (X5):

The formulation labeled as X5 has been identified as the optimal choice for the oral disintegration strip containing Levetiracetam. This selection is based on a comprehensive assessment of various parameters.

8.3 Preparation Method:

The optimized formula was successfully prepared using the solvent casting method, indicating its feasibility and applicability for producing the desired oral disintegration strip.

8.4 Key Performance Indicators:

- Thickness Test:

The optimized formula exhibited an optimum thickness, ensuring practical handling and administration.

- Tensile Strength and Folding Endurance:

These mechanical properties were within acceptable limits, indicating the formulation's robustness and durability.

- Moisture Content:

The formulation maintained an appropriate moisture content, essential for stability and shelf life.

- Dissolution Test:

The optimized formula demonstrated efficient dissolution with a shorter time required, enhancing its potential for a quick onset of action.

8.5 Future Implications:

The success of the optimized formula suggests its potential for further clinical evaluation and application in real-world therapeutic settings. Continued research and development may lead to the incorporation of this formulation into epilepsy treatment protocols.

In summary, the oral disintegration strip containing Levetiracetam, particularly the optimized formula X5, stands as a promising pharmaceutical option, offering both efficacy and user-friendly attributes. The positive outcomes from various evaluations support its advancement towards broader clinical utilization in the management of epilepsy.

9. Future Scope

The future scope of Oral Disintegration Strips (ODS) presents promising opportunities in various sectors, including Cosmeceuticals, Nutraceuticals, and Pharmaceuticals. Several factors contribute to the potential growth and acceptance of ODS technology, leading to its commercialization and application in diverse areas. Here are some key aspects of the future scope:

9.1 Commercialization Potential:

The increased commercialization of ODS brands holds the key to future acceptance and growth. As more companies invest in the development and marketing of ODS formulations, the technology is likely to become more widely recognized and adopted.

9.2 Patient Compliance Improvement:

ODS technology offers a convenient and patient-friendly dosage form, contributing to improved patient compliance. The ease of administration, quick dissolution, and potential for masking bitter tastes make ODS an attractive option for patients, especially those who may have difficulty swallowing traditional dosage forms.

9.3 Versatility in Applications:

ODS technology's versatility makes it applicable across different industries, including Cosmeceuticals (cosmetics with pharmaceutical benefits), Nutraceuticals (products combining nutritional and pharmaceutical elements), and Pharmaceuticals. The adaptability of ODS formulations to various active ingredients enhances their potential in addressing diverse health and wellness needs.

9.4 Innovation in Drug Delivery:

ODS technology presents opportunities for innovation in drug delivery systems. As researchers explore and optimize ODS formulations, new therapeutic options and drug delivery strategies may emerge, catering to specific patient needs and therapeutic requirements.

9.5 Cosmeceutical Applications:

The use of ODS in the Cosmeceutical industry can lead to the development of skincare and cosmetic products with enhanced delivery of active ingredients. This can offer benefits such as improved skin penetration and targeted delivery, contributing to the efficacy of cosmetic formulations.

9.6 Nutraceutical Potential:

ODS can be applied in the Nutraceutical sector to create oral strips delivering essential nutrients, vitamins, and other bioactive compounds. This aligns with the growing trend of convenient and novel delivery forms in the nutritional supplement industry.

9.7 Pharmaceutical Advancements:

Continued advancements in ODS technology may lead to the development of novel pharmaceutical products with enhanced bioavailability, improved therapeutic outcomes, and reduced side effects. ODS formulations may find applications in a wide range of therapeutic areas.

In summary, the future of ODS technology looks promising with its potential for commercialization, patient-centric benefits, and versatility across different industries. Ongoing research, innovation, and market adoption will likely shape the landscape of ODS, positioning it as a valuable option in drug delivery and wellness products.

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